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

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Highlights

- LOS and VLOSP are characterised by diffuse and mildly progressive cognitive dysfunction
- The nature and progression of neuropsychological deficits differ from changes in neurodegenerative processes
- Neurobiological underpinnings consist of generalized brain atrophy and increased ventricle-to-brain ratio, white matter pathology and functional changes suggesting a fronto-subcortico-temporal pattern of impairment

- The contribution of neurobiological mechanisms in LOS and VLOSP may be modulated by premorbid (psychosocial and genetic) vulnerability
- More research is needed to draw firm conclusions

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

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

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 (Binbay et al., 2012; Howard et al., 2000; Sharma et al., 2014). 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 (Howard et al., 2000). 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 (Howard et al., 2000; Palmer et al., 2001).

The one-year prevalence of schizophrenia in individuals aged 45 to 65 years is 0.6% (Keith et al., 1991), whereas the community prevalence for VLOSLP ranges from 0.1% to 0.5% (Howard et al., 2000). 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 (van Os et al., 1995). 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 (Howard et al., 2000). 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 (Howard et al., 1997). Finally, clinical features differ, with the most striking differences between AOS and VLOSLP (Kerssens et al., 2006). 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 (Hanssen et al., 2015). 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 (Howard et al., 2000). 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 (Frith, 1996). 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 (Green et al., 2015).

Some researchers have disputed the diagnostic validity of LOS or VLOSLP (Andreasen, 1999; Brodaty et al., 2003). 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 (Brendan and Petersen, 2007; Fichman et al., 2011), frontotemporal degeneration (FTD) with important executive dysfunction and impaired social cognition in the behavioral variant (Hutchinson and Mathias, 2007), or dementia with Lewy bodies (LBD) which is initially primarily characterized by perceptual and executive deficits (Collerton et al., 2003) 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 (Savva et al., 2009). 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 (Kørner et al., 2009), does not invariably predict cognitive or functional decline (Lagodka and Robert, 2009; Rabins and Lavrisha, 2003). 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 (Frith, 1996; Zakzanis et al., 2001), 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 (Frith, 1996; Phillips et al., 1997). 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 (Ruff, 2003). 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 (Harvey, 2012). Notably, correlations may sometimes be low or absent as brain changes evident in imaging 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 (Harvey, 2012). 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 (Ruff, 2003). 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 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 (Howard et al., 2000; Iglewicz et al., 2011; Naguib, 1992). 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 that 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, AOS and neurodegeneration. First, cross-sectional data will be summarized (Table 1). Next, the

longitudinal course of (socio)cognitive functioning will be enlightened (Table 2). Demographic characteristics of participant groups are described in more detail in Table 1 and 2. In a second part of the review, there will be an in-depth discussion of neurobiological findings in LOS/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 (Grady and Craik, 2000). 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 (Almeida et al., 1995a, b; Henderson et al., 1998; Jeste et al., 1995; Miller et al., 1991; Sadek et al., 2012). There were only three exceptions. In one small study by Phillips et al. (1997) 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 (Girard et al., 2011) found no significant differences in basic cognitive functioning of LOS/VLOSLP (n=15) and healthy controls (n=11). Thirdly, Almeida and colleagues 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 (Almeida et al., 1995a, b). 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 in 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 (Girard et al., 2011; Huang and Zhang, 2009; Jeste et al., 1995; Smeets-Janssen et al., 2013), 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 and colleagues (1997) observed inferior performances in a mixed group of LOS and VLOSLP compared with AOS. Hanssen et al. (2015), 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 schizophrenia with average age onset and that may slightly be aggravated by age-related declines. Importantly, differences in cognitive profile have been described in chronic AOS 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 (Kern et al., 2011). 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 (Savla et al., 2013). First episode psychosis, conversely, is specifically associated with reduced processing speed and verbal learning according to a recent meta-analysis (Mesholam-Gately et al., 2009). 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 (Lewandowski et al., 2011). Even though functioning in many cognitive domains shows 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 (Szoke et al., 2008). Moreover, age has been described as a potential moderator of the quality and quantity of cognitive impairment in schizophrenia with average age onset (Fioravanti et al., 2012; Irani et al., 2011; Rajji et al., 2009). 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 (Irani et al., 2011). 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 (Heaton et al., 1994; Hopkins and Roth, 1953; Palmer et al., 2003; Zakzanis et al., 2003) and (the behavioral variant of) FTD (Zakzanis et al., 2001). Also, vascular cognitive impairment (VCI) with concomitant psychosis was studied (Hopkins and Roth, 1953). 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 et al. (2014) 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 (1994) 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 (1953), Palmer et al. (2003) and Zakzanis et al. (2001; 2003) – 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 (Almeida et al., 1995a; Heaton et al., 1994; Jeste et al.; 1995; Moore et al., 2006; Östling et al., 2004; Sachdev et al., 1999a; Vahia et al., 2010). Premorbid intelligence, however, appeared within the average range for both clinical and control groups (Almeida et al., 1995a; Henderson et al., 1998; Phillips et al., 1997; Smeets-Janssen et al., 2013). 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. (1997; 1999a) 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 (Sachdev et al., 1999a). Studies that compared LOS and VLOSLP to young and older AOS also found similar current intellectual capacities (Hanssen et al., 2015; Heaton et al., 1994; Jeste et al., 1995). 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 (Hopkins and Roth, 1953). 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 (Hopkins and Roth, 1953). Senile psychosis (a neurodegenerative condition, not further specified) led to inferior test results on all three tasks compared with LOS/VLOSLP (Hopkins and Roth, 1953). Zakzanis and colleagues (2001) 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 (Heaton et al., 1994; Henderson et al., 1998; Jeste et al., 1995; Miller et al., 1991; Naguib and Levy, 1987; Sachdev et al., 1999a; Vahia et al., 2010). Impairments are similar to those noticed in AOS for motor speed (Jeste et al., 1995), information processing speed (Sachdev et al., 1999a) and

complex perceptual-motor speed (Heaton et al., 1994). Still, Vahia and colleagues (2010) 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 (Almeida et al., 1995a; Brichant-Petitjean et al., 2013; Hanssen et al., 2015; Heaton et al., 1994; Sachdev et al., 1999a). Furthermore, a cross-sectional study comparing attention in AOS, LOS and VLOSLP found significantly more impairment on vigilance in VLOSLP participants compared with LOS (Hanssen et al., 2015). 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 (Hanssen et al., 2015; Heaton et al., 1994; Jeste et al., 1995; Sachdev et al., 1999a; Smeets-Janssen et al., 2013). A comparison with neurodegenerative conditions showed that FTD subjects performed significantly better on the auditory attention span in comparison with LOS (Zakzanis et al., 2001). 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 (Almeida et al., 1995a; Brichant-Petitjean et al., 2013; Moore et al., 2006; Sachdev et al., 1999a). Furthermore, cognitive flexibility and abstraction are deficient in studies that included LOS or a mixed group of LOS and VLOSLP (Girard et al., 2011; Heaton et al., 1994; Jeste et al., 1995; Sachdev et al., 1999a). Concurrently, logical reasoning shows impairment in VLOSLP (Östling et al., 2004), although Phillips and colleagues (1997) 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 (Almeida et al., 1995a, b; Jeste et al., 1995). Verbal fluency is also reported to be impaired in LOS and a mixed group (Almeida et al., 1995a; Brichant-Petitjean et al., 2013). Still, Almeida and colleagues (Almeida et al., 1995b), 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 (Smeets-Janssen et al., 2013). 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 (Hanssen et al., 2015; Heaton et al., 1994; Jeste et al., 1995; Sachdev et al., 1999a; Smeets-Janssen et al., 2013). 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 (Brichant-Petitjean et al., 2013; Jeste et al., 1995; Vahia et al., 2010). 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 (Zakzanis et al., 2003). On the other hand, FTD subjects scored worse on abstraction, cognitive flexibility and verbal fluency than LOS subjects (Zakzanis et al., 2001).

Verbal/visual learning and memory. Studies with respect to learning and consolidation of verbal or visual information have yielded mixed results. Naguib and Levy (1987) 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 (Almeida et al., 1995a; Brichant-Petitjean et al., 2013; Jeste et al., 1995; Miller et al., 1991; Sachdev et al., 1999a; Vahia et al., 2010). Additionally, Henderson et al. (1998) have reported impairment in a mixed group of LOS/VLOSLP on episodic memory, using the Episodic Memory Test (EMT). However, Girard et al. (2011), in a relatively small sample, did not find impairment on verbal learning or consolidation in a comparable mixed group. Similarly, Heaton et al. (1994) and Östling et al. (2004) 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) (Brichant-Petitjean et al., 2013). Interestingly, Almeida and colleagues (1995b) 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 suggest an impairment.

In line with this, a visual or verbal encoding and consolidation deficit has often been observed in AOS (Jahshan et al., 2010) as well as LOS and VLOSLP (Hanssen et al., 2015; Heaton et al., 1994; Sachdev et al., 1999a). Some researchers found a superior performance in LOS and mixed groups compared to AOS with respect to immediate recall (Brichant-Petitjean et al., 2013; Girard et al., 2011) or delayed recall (Jeste et al., 1995). Vahia et al. (2010) 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 (2003) 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 et al. (2014) found greater consolidation deficits for visual and verbal information in AD as opposed to VLOSLP. Heaton et al. (1994) 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. (2003), 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 (Zakzanis et al., 2001). 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. (1994) 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 (Jeste et al., 1995). 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 (Vahia et al., 2010). 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. (1994) and Jeste et al. (1995) 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 (Heaton et al., 1994), 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 (Girard et al., 2011; Östling et al., 2004). Östling et al. (2004) 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 (Vahia et al., 2010). Concurrently, impairments with respect to spatial relation perception, auditory and tactual perception have been noticed in LOS and VLOSLP (Heaton et al., 1994; Jeste et al., 1995; Phillips et al., 1997). Phillips et al. (1997), 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. (1994) and Jeste et al. (1995) 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 (Jeste et al.,

1995; Sachdev et al., 1999a). One study noticed a superior performance in LOS compared with AOS subjects on Block design, but not on Picture completion (Vahia et al., 2010). 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 (Zakzanis et al., 2001). There were no clear differences in performance on perceptual tasks when comparing LOS with AD in one study (Heaton et al., 1994). Still, Harris et al. (2014) did observe impairment in visuoperceptual skills, specifically object recognition, in VLOSLP compared with AD subjects.

Social cognition. Phillips et al. (1997) 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 (Moore et al., 2006). 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. (2013) 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 (Smeets-Janssen et al., 2013). 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 (Adenzato et al., 2010).

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 (Hanssen et al., 2015). Also, social cognition appears to show less impairment. Still, other cognitive domains, such as language and perception, might be similarly affected in late onset psychosis. 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 (Brodaty et al., 2003; Laks et al., 2006; Palmer et al., 2003). However, Hymas et al. (1989) 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. (2003) 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 (1987) 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 were 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 (Palmer et al., 2003). 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 (Mazeh et al., 2005; Palmer et al., 2003) 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. Furthermore, 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 (Birur et al., 2017). 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 (Birur et al., 2017).

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. 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 (Breitner et al., 1990) or older (Sachdev et al., 2000; Symonds et al., 1997) healthy controls or with studies that do not specify whether the ages are matched, even though older participants are included as healthy controls (Casanova et al., 2002; Casanova, 2003; Corey-Bloom et al., 1995; Coura and Elkis, 1997; Lesser et al., 1993).

Volumetric brain changes: atrophy and/or dysgenesis. An increased ventricle to brain ratio (VBR) and larger third ventricles have repeatedly been reported in LOS (Barak et al., 2002; Corey-Bloom et al., 1995; Lesser et al., 1993; Rabins et al., 1987; Rabins et al., 2000), even though the extent of the increase may show differential correlations with the phenomenology of the disease. For instance, Howard et al. (1994) 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 (Miller et al., 1989). Interestingly, Barta et al. (1997) 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 (Pearlson et al., 1993).

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 (Barak et al., 2002; Casanova, 2010; Corey-Bloom et al., 1995; Coura and Elkis, 1997). Only one smaller study reported no significant alterations on the MRI's of LOS participants compared to normal controls (Reeves and Struve, 2003).

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 (Barta et al., 1997; Casanova, 2010; Sachdev et al., 2000). As opposed to the pattern observed in Alzheimer's disease, the anterior superior temporal gyrus volume appeared smaller in LOS than in normal controls (Barta et al., 1997). Again, the authors state that this is similar to neural changes in AOS. Coincidently, Rabins et al. (2000) found more temporal lobe and subcortical atrophy in LOS than in normal controls. Moreover, Howard et al. (1992a; 1992b) 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 (Denihan et al., 2000). Contrary to observations in LOS, disease duration appeared positively associated with a reduction in the temporal pole in AOS (Egashira et al., 2014). Additionally, even though the pattern of atrophy described by Rabins et al. (2000) 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 (Rabins et al., 2000). 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 (Egashira et al., 2014). Even though Sachdev and Brodaty (1999) 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. (2002) observed more pronounced cerebellar atrophy in VLOSLP than controls. Still, thalamic volumes in LOS appear greater than those in normal controls and AOS

participants (Corey-Bloom et al., 1995). Moreover, Egashira et al. (2014) found larger grey matter volumes of the left precuneus in LOS as opposed to healthy controls.

Casanova and Lindzen (2003) 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. 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. 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 (Breitner et al., 1990; Lesser et al., 1993; Miller et al., 1991; Sachdev and Brodaty, 1999). White matter hyperintensities (WMH) and lesions (WML) have been observed in temporoparietal, frontal and occipital regions (Breitner et al., 1990; Miller et al., 1991), in the thalamus (Sachdev and Brodaty, 1999) and periventricular (Sachdev and Brodaty, 1999; Sachdev et al., 1999a). There was some inconsistency in findings with regard to subcortical and frontal areas (Sachdev and Brodaty, 1999; Sachdev et al., 1999a; Su et al., 2001), with some studies reporting a relatively preserved structure of the basal ganglia. Su et al. (2001), 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. (1995) 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. (2000) and Symonds et al. (1997) 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) (Chen et al., 2013; Jones et al., 2005). 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 (Jones et al., 2005). However, Chen et al. (2013) 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 (Miyaoka et al., 2001; Miyaoka et al., 2005; Sachdev et al., 1999b; Suzuki et al., 2002), which points to changes in brain metabolism. These could only partially be explained by neuroleptic drug use. Additionally, Olichney et al. (1998) 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 (Olichney et al., 1997).

SPECT studies showed significant differences in regional cerebral blood flow in LOS compared to AOS and healthy controls (Lesser et al., 1993; Sachdev et al., 1997; Wake et al., 2016), 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 (Lesser et al., 1993). 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 (Sachdev et al., 1997). 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 (Wake et al., 2016). The authors state that there is a significantly differing pattern of brain perfusion in AOS and LOS. In another study, Howard et al. (1993) 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. (2013) 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. (2002) observed tau positive glial tangles but no or very little amyloid deposit (typical of Alzheimer's disease), in LOS. Coincidently, Bozikas et al. (2002) 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 (2003) 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 (Casanova and Lindzen, 2003).

These could best be explained, according to the authors, as a dying back neuropathy. Finally, Nagao et al. (2014) 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 (Howard et al., 2000). 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 two groups (see Table 3). Only one study compared LOS and VLOSLP directly (Hanssen et al., 2015). 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 its comparison with AOS, normal aging or neurodegeneration and not research focusing solely on the neuropsychology and neurobiology of AOS or neurodegeneration as this is a very extensive literature and it has recently been discussed in depth by several authors (Fatouros-Bergman et al., 2014; Fioravanti et al., 2012; Irani et al., 2011; Nuechterlein et al., 2014; Rajji et al., 2009; Savla et al., 2013). Hence, we used recent meta-analyses to complement the study results of research directly comparing LOS, VLOSLP and AOS. No obvious inconsistencies were found between results from comparative studies on LOS, VLOSLP and AOS or neurodegeneration versus the literature solely focusing on AOS or neurodegeneration. 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 (Antonova et al., 2004), 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 (Antonova et al., 2004). 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 (Howard et al., 1995). 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 (Almeida et al., 1995a).

Several brain abnormalities have been described in LOS and VLOSLP in areas that are especially involved in executive function and social cognition (Kerns et al., 2008; Pinkham et al., 2003), 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 (Fischer et al., 2017). 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 (Green et al., 2015), associated with a neural network involving the prefrontal cortex and amygdala (Pinkham et al., 2003). Hence, researchers have suggested that a relatively spared social cognitive functioning may be a protective factor modulating the age at onset of psychotic symptoms (Smeets-Janssen et al., 2013). 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 (Pinkham et al., 2003). 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 (Coltheart, 2010). Coltheart (2010) 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 (Mesholam-Gately et al., 2009). These impairments are related to prefrontal (PFC) and medial 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 (Sachdev et al., 1997).

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 (Barch, 2005). 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 (Brébion et al., 2013; Ranganath et al., 2008). 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, which usually affects the (pre)frontal, subcortical and temporal areas. 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 (Duman and Monteggia, 2006; Lupien et al., 2009; McEwen, 2007). 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 average age onset schizophrenia, which also leads to better occupational and marital histories (Howard et al., 1997; 2000).

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 (Howard et al., 2000). 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 – seems to trigger an earlier existing 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 (Nuechterlein et al., 2014).

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Figure captions

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

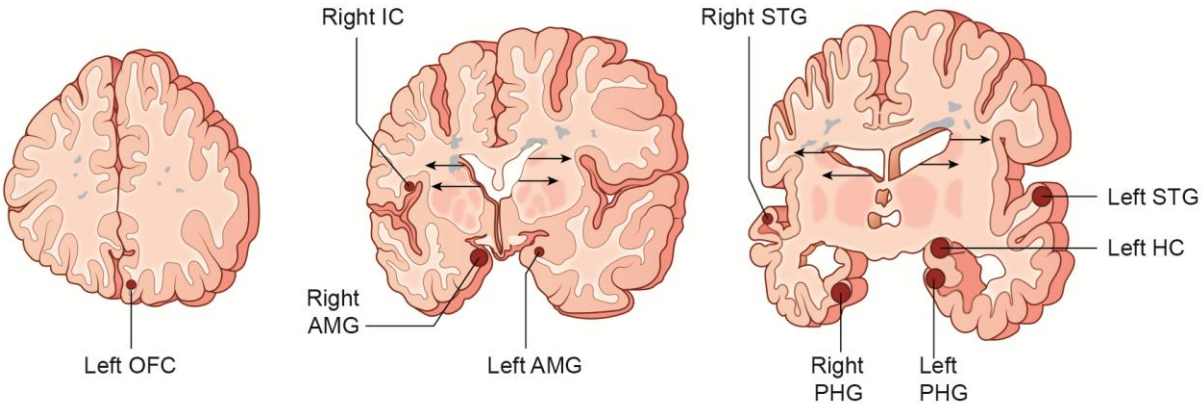

Table 1

Overview of cross-sectional studies on cognitive functioning in LOS and VLOSP

Author(s)	Participants	Age	Instruments	Treatment context	Findings
Almeida et al. (1995a)	Late paraphrenia Onset of psychosis after 55 years N=47 Healthy controls N=33	M: 77.36 CI: 75.50-79.22 M: 75.69 CI: 73.00-78.39	MMSE, CAMCOG, WAIS-R, NART, RTF, RTW, VFT, CEIDST, CSWMT, CTLT	Hospitalized	Individuals with late paraphrenia performed significantly worse compared to normal controls on MMSE, CAMCOG, WAIS-R, spatial span capacity, delayed matching to sample, recognition of faces, executive function (Verbal fluency, Computerized Extra and Intra Dimensional Shift Task, Computerized Spatial Working Memory Task, Computerized Tower of London Task). There was no significant difference on recognition of words, simultaneous matching to sample, and learning as assessed with a recurring digit and spatial supraspan task.
Almeida et al. (1995b)	Late paraphrenia Onset of psychosis after 55 years N=47 Healthy controls N=33	M: 77.36 CI: 75.50-79.22 M: 75.69 CI: 73.00-78.39	Cf. Almeida et al. (1995a)	Hospitalized	There were two cognitive subtypes in late paraphrenia. Cluster 1 (N=24): only impairment on extra dimensional set shift and planning abilities, suggesting a more restricted executive deficit. Cluster 2 (N=23): widespread cognitive impairment and executive dysfunction. There was no evidence of dementia.
Brichant-Petitjean et al. (2013)	LOS N=25 AOS	M: 50.88 SD: 9.16 M: 35.36	RCF, DS Fw, DS Bw, VFT	Outpatients	LOS performed better than AOS on the Digit Span, RCF and phonemic verbal fluency. LOS scored worse on Digit Span and verbal fluency than healthy controls.

	N=44 Controls N=23	SD: 8.25 M:46.87 SD:9.68			
Sadek et al. (2012)	LOS N=50 Healthy controls N=50	M:72.5 SD:8.29 M:71.99 SD:2.2	CAMCOG, WAIS	No specifications	Scores on CAMCOG and WAIS were impaired in LOS compared with normal controls. All cognitive domains were affected.
Girard et al. (2011)	LOS N=15 AOS N=17 Healthy controls (2 groups) N=11 N=11	M:75.6 SD:4.00 M:65.53 SD:9.05 Age matched with AOS, no further specifications	DRS-II, MMSE, WAIS-III: DS Fw, DS Bw, CVLT-II, VFT, CDT, Stroop from D-Kefs, TMT from D-Kefs	Hospitalized	AOS showed more memory (encoding) and executive problems compared with controls. There was not a significant difference between LOS and controls after controlling for age and education. However, LOS showed executive dysfunction in comparison with normative data provided in the test manual.
Hanssen et al. (2015)	AOS N=24 LOS N=24 VLOSP N=28 Healthy controls N=290	M:27.37 Range: 26.47-28.24 M:58.13 Range: 53.02-63.23 M:75.68 Range: 72.56-78.80 M:37.55	CAMCOG (for LOS and VLOSP), GWLT, CPT, RST, shortened version of WAIS-III (Information, Block Design, Digit Symbol Coding, Arithmetic) Or RSPM (older participants)	Hospitalized and outpatients	The three groups did not differ with respect to IQ, verbal memory or executive function. VLOSP performed better than LOS on the CAMCOG total score (general cognitive abilities). VLOSP showed significantly less accurate responses on an attention accuracy task (vigilance) compared with LOS.

		Range: 35.50-39.59			
Hopkins & Roth (1953)	Late paraphrenia N=12 Acute confusion with psychosis (delirium) N=14 Arteriosclerotic psychosis (vascular cognitive impairment with psychosis) N=14 Affective psychosis (affective disorder with psychosis) N=30 Senile psychotics (Alzheimer's disease with psychosis) N=14	M:75.6 Range:65-86 M:71.0 Range:61-80 M:76 Range:61-80 M:73.4 SD:70-85 M:78.1 SD:67-88	Vocabulary subtest from the WBS/MHVT, PM 1938 version Information test	Hospitalized	Mean scores for paraphrenics and for the confusional patients who finished all three tests were comparable to those of the affective group, whereas the arteriosclerotic group scored consistently lower. Though their score on vocabulary was comparable to that of the affective psychosis group, they performed worse on Matrices and Information. The arteriosclerotic group still scored higher than the senile psychosis group. However, the difference is only significant for the Information test.
Harris, Kotsopoulos & Yamin (2014)	Late onset delusional disorder (LODD) N=19 AD N=20	M:83.47 SD:6.45 M:79.60 SD:6.27	MMSE, NART, WAIS-IV, subtests of WMS-IV: Logical memory I & II, Visual reproduction I & II	Hospitalized and outpatients	There were no significant differences on general cognitive abilities or premorbid intelligence: LODD MMSE 25,61 (2,33) AD MMSE 24,47 (2,23) LODD NART 102,83 (8,83) AD NART 109,59 (9,67)

			HVLT, Stroop, TMT, AI, COWAT, AVF, BNT, RCF copy		LODD showed moderate impairment in conceptual reasoning, visual object recognition, processing speed, confrontation naming. Compared to AD the LODD group showed poorer visuoperceptual skills (object recognition) and better capacity to consolidate visual and verbal information.
Heaton et al. (1994)	Healthy controls N=38 AD N=42 AOS young N=85 AOS old N=35 LOS N=22	M:65.7 SD:8.5 M:65.6 SD:8.5 M:30.4 SD:7.4 M:55.9 SD:9.1 M:59.0 SD:6.5	HR, AST, BNT, COWAT, WAIS-R: block design, object assembly, digit symbol subtests, digit span, arithmetic subtests, TMT A&B, TPT, DVT, CT, WCST, RT, SSPT, DVT, FMT, SMT, CVLT, FTT, GP, HD	Hospitalized and outpatients	The estimated IQ was within the average range for all groups, though normal controls performed significantly better than all other groups. AOS young, AOS old and LOS had comparable neuropsychological profiles. They demonstrated mild to moderate impairments on verbal ability, complex perceptual-motor speed, abstraction and flexibility of thinking, attention, learning, sensory abilities, motor skills. AD showed less efficient learning of visual and verbal information than the old AOS and LOS group, and they showed rapid forgetting of both visual and verbal information compared to all other groups.
Henderson et al. (1998)	Sample of 935 both community dwelling older adults and older adults in sheltered accommodation (age > 70 years) 65 subjects of this sample experienced psychotic symptoms	M:76.7 SD:5.1 M:78.9 SD:6.5	MMSE, SLMT, EMT, NART	Community dwelling and sheltered accommodation	NART scores were comparable in psychotic and non-psychotic elderly. MMSE scores were significantly higher in non-psychotic elderly. Psychotic elderly also showed impaired cognitive speed and episodic memory.

	and 25 of these also had dementia or moderate cognitive impairment, which leaves 40 subjects with non-organic psychosis				
Huang & Zhang (2009)	LOS N=23 AOS N=29	M:65.3 SD:4.7 M:66.0 SD:5.5	MMSE	Hospitalized	MMSE scores were markedly impaired. They did not differ significantly in both groups.
Jeste et al. (1995)	LOS N=25 AOS N=39 Normal controls N=35	M:60.4 SD:7.6 M:58.1 SD:8.8 M:65.8 SD:7.8	DRS, MMSE, WAIS-R, WCST, TMT B, SMT, FMT, CVLT, GP, AST, SPE: spatial relations	Hospitalized and outpatients	LOS and AOS were impaired on almost all neuropsychological measures compared with normal controls: verbal IQ, performance IQ, abstraction and flexibility, shifting, motor speed, learning and consolidation of both visual and verbal information, perception and language. Still, AOS showed more perseverative mistakes compared with LOS. Also, the delayed recall was less impaired in LOS than in AOS. Moreover, LOS performed comparable to normal controls on delayed recall, perceptual motor skills and sensory abilities.
Miller et al. (1991)	LOS N=24 Healthy controls N=72	M: 60.1 SD: 10.1 M:61.6 SD:10.0 LOS	MMSE, WAIS-R, Logical Memory and Visual reproduction of the WMS, RCF, WCST, Stroop, ACT,	Hospitalized and outpatients	MMSE scores were significantly higher in healthy controls than in LOS subjects. Performance on almost all neuropsychological tests was worse in LOS compared to healthy controls. Only the WAIS-R Digit Span and the WMS Visual reproduction were comparable. After

	21 matched pairs were used for analysis of neuropsychological data	M:59.0 SD:8.8 Healthy controls M:59.1 SD:9.0	VFT (FAS), WRMT for words and faces		controlling for multiple comparisons, the IQ scores, executive measures (WCST categories, FAS, ACT, Stroop time) and verbal memory tasks (RMT-words, WMS Logical memory still showed significant differences, whereas attention (Digit span) or visual spatial skills (RCF) seemed relatively preserved.
Moore et al. (2006)	VLOSP N=29 LOD (depression) N=30 Healthy controls N=30	M:76.90 SD:5.99 M:77.07 SD:8.52 M:75.73 SD:5.59	WASI: vocabulary, matrix reasoning, DS Bw, Mentalizing task (Snowden et al. unpublished): first and second order false belief, first and second order deception, BiaJ	Hospitalized and outpatients	The comparison group scored higher than both clinical groups on the WASI and the digit span backwards. Performance on the WASI (IQ) correlated significantly with mentalizing tasks. VLOSP performed worse on deception but not on false belief mentalizing tasks after controlling for general intelligence. There were no significant differences on probabilistic reasoning.
Naguib & Levy (1987)	LOS N=43 Healthy controls N=40	M:75.27 SD:6.29 M:75.85 SD:8.64	MTS: memory and orientation, DCT, DSST	Hospitalized and outpatients	LOS subjects scored lower on all tests, but the difference was only significant for the MTS (memory and orientation) and DCT (psychomotor speed).
Östling et al. (2004)	Non-demented, community dwelling 85-year olds N=261	M:85	SRB 1, SRB 2, SRB 3, PSIF, TPMT , DS Fw, DS Bw, CDT, Coin Test , MIR, PRT, TWMT	Community dwelling	51 (14.7%) participants showed paranoid ideation or psychotic symptoms. 141 (67.1%) of the mentally healthy and 20 (39.2%) of the individuals with psychosis were alive and non-demented after 3 years.

					Psychotic symptoms and paranoid ideation were associated with lower performance compared with the mentally healthy on SRB1, SRB2, SRB3, PSIF, Clock test, MIR Memory test (recognition), Prose recall test, Ten word memory test. After controlling for possible confounders and incident dementia or terminal decline, there was a worse performance on SRB 1, SRB 2, SRB 3 and the Clock Test. Hence, performance was most affected on general cognitive abilities (verbal ability, logical reasoning, spatial ability), while other visual or verbal memory test performance was no longer associated with paranoid ideation and psychotic symptoms.
Phillips et al. (1997)	VLOSP N=3 Healthy controls N=8	Ages 80, 86, 75 M:79 Range: 66-86	NART, MMSE, JFE (Ekman & Friesen, 1976), WRMT for Faces, BFM, RFF, VOSP, Verbal reasoning tests	Hospitalized and outpatients	All subjects had similar IQ scores (above average). MMSE scores ranged from 26-30 with an average of 28 in normal controls. They were 28, 29 and 28 in the clinical group. Patients performed well on most (facial (expression)) perceptual tasks. However, there was impaired matching of unfamiliar faces and famous face recognition in two VLOSP subjects and impaired silhouette recognition in all VLOSP subjects. Increasing the emotional content of logical reasoning problems also had a significant effect on the deluded subject's reasoning but not that of the normal controls.
Sachdev et al. (1999)	LOS N=28 AOS N=24	M:73.6 SD:9.7 M:62.1 SD:8.3	NART, WAIS-R: picture completion, block design, similarities, comprehension, vocabulary, WMS-R:	Hospitalized and outpatients	There was a significant difference with regard to premorbid intelligence. LOS and AOS perform worse than healthy controls. There was no significant difference on vocabulary (WAIS-R) after correcting for education, and on similarities, mental control, verbal paired associates, digit span backwards after controlling for age.

	Healthy controls N=30	M:71.8 SD:7.4	mental control, figural memory, logical memory I & II, verbal paired associates, visual reproduction I & II, digit span , WCST, COWAT, AHPQ		LOS and AOS performed more poorly on tests assessing speed of information processing, verbal and figural memory, visuospatial function, attention, working memory and frontal executive functioning compared with normal controls. LOS and AOS did not significantly differ from each other on neuropsychological measures.
Sachdev et al. (1997)	LOS N=15 AOS N=7 Healthy controls N=27 Cf. Sachdev et al. (1999)	M:73.2 SD:10.6 M:54.8 SD:5.3 M:71.7 SD:6.4	MMSE, NART, WAIS-R: Picture Completion, Block Design, Similarities, Comprehension, Vocabulary, WISC: Mazes, WMS-R: Mental Control, Figural memory I & II, Verbal Paired Associates, Visual reproduction I & II, Digit Span, WCST, COWAT, AHPQ	Hospitalized and outpatients	LOS had lower MMSE scores than the other two groups. LOS had lower NART scores than controls. Other neuropsychological variables were not compared between groups. They had a low correlation with perfusion. Only MMSE and WMS Logical memory correlated significantly with temporal lobe (hypo)perfusion. This was specifically so for LOS.
Smeets-Janssen et al. (2013)	AOS N=15 LOS	M:65.5 SD:4.7 M:67.3	Hinting task, MMSE, FAB, NART	Hospitalized and outpatients	There were no significant differences on premorbid intelligence, general cognitive ability or FAB (frontal assessment battery: executive function such as mental flexibility, sensitivity to

	N=15	SD:5.8			interference, conceptualization, inhibitory control, environmental autonomy).
	Healthy controls N=30	M:66.7 SD:4.4			AOS scored significantly lower on the Hinting Task than LOS and healthy controls.
Vahia et al. (2010)	LOS N=110	M:57.6 SD:8.7	WAIS-R or WAIS-III: Information, Vocabulary,	Hospitalized and outpatients	LOS and AOS groups were both cognitively impaired in comparison with the normal controls. There were no significant differences between AOS and LOS subjects with respect to crystalized verbal knowledge (Information, Vocabulary, Similarities) or auditory working memory (Arithmetic). The LOS group performed better on processing speed, abstraction, cognitive flexibility and verbal memory than the AOS group. There was a superior performance of the LOS group compared with the AOS group on one of the perceptual tasks (Block Design) but not on the other (Picture Arrangement).
	AOS N=744	M:51.0 SD:8.3	Similarities, Picture Arrangement, Block Design, mental		
	Healthy controls N=359	M:59.8 SD:14.5	Arithmetic, Digit Symbol, WCST, CVLT		
Zakzanis et al. (2003)	LOS N=32	M:58.84 SD:8.57	WAIS-R, WMS-R: Logical memory immediate and	Hospitalized and outpatients	AD showed superior ability on all of the neuropsychological tasks except the WMS-II logical memory delayed recall and the CVLT long-delay free recall.
	AD N=32	M:78.75 SD:8.30	delayed recall, TMT A and B, CVLT: short delay and long delay free recall		There are significant differences between both patient groups on WMS-R Logical memory immediate recall. AD performed better than LOS. TMT part B showed significantly worse performance in LOS compared with AD. However, effect sizes were small. Evaluation of effect sizes showed that CVLT short and long delay free recall, WAIS-III Similarities subtest had the greatest sensitivity to discriminate between AD and LOS. Tests with low differentiating ability were WAIS Block Design, TMT B, WAIS III Full Scale IQ.

Zakzanis et al. (2001)	LOS N=32	M:57.84 SD:8.57	WAIS-R, PM, RCF, HVOT, CVLT, WCST, VFT (FAS, animals), WMS: Logical Memory, Visual Reproduction, TMT A & B	Hospitalized and outpatients	There were significant differences on WAIS-R Digit Span (LOS < FTD), WCST categories (FTD < LOS), Verbal fluency FAS and animals (FTD < LOS). Effect sizes were calculated and suggest that WAIS-R Vocabulary (LOS < FTD), Information (LOS < FTD), Comprehension (LOS < FTD) and HVOT (LOS < FTD) can distinguish more than 60% of patients with FTD from patients with LOS, even though there were no statistically significant differences between groups. Effect sizes suggest that WCST and verbal fluency tasks cannot reliably discriminate patient groups.
	FTD N=12	M:61.58 SD:8.04			

Note. MMSE, Mini Mental State Examination; CAMCOG, Cambridge Cognitive assessment battery; WAIS-R, Wechsler Adult Intelligence Scale-Revised; NART, National Adult Reading Test; RTF, Recognition Test for Faces; RTW, Recognition Test for Words; VFT, Verbal Fluency Test; CEIDST, Computerized Extra and Intra Dimensional Shift Task; CSWMT, Computerized Spatial Working Memory Task; CTLT, Computerized Tower of London Task; RCF, Rey Complex Figure; DS Fw, Digit Span Forward; DS Bw, Digit Span Backward; DRS, Dementia Rating Scale; CVLT, California Verbal Learning Test; CDT, Clock Drawing Test; SCWT, Stroop Colour Word interference Test; TMT, Trail Making Test; GWLT, Groningen Word Learning Test; CPT, Continuous Performance Test; RST, Response Shifting Task; (RS)PM, (Raven Standard) Progressive Matrices; WBS, Wechsler-Bellevue Scale; MHVT, Mill Hill Vocabulary Test; WMS, Wechsler Memory Scale; HVLT, Hooper Verbal Learning Test; AI, Army Individual test battery; COWAT, Controlled Oral Word Association Test; AVF, Animal Verbal Fluency; BNT, Boston Naming Test; HR, Halstead-Reitan battery; AST, Aphasia Screening Test; TPT, Tactual Performance Test; DVT, Digit Vigilance Test; CT, Category Test; WCST, Wisconsin Card Sorting Test; RT, Rhythm Test; SSPT, Speech Sounds Perception Test; FMT, Figure Memory Test; SMT, Story Memory Test; FTT, Finger Tapping Test; GP, Grooved Pegboard; HD, Hand Dynamometer; SLMT, Symbol Letter Modalities Test; EMT, Episodic Memory Test; SPE, Sensory Perceptual Examination; ACT, Auditory Consonant Trigrams; WRMT, Warrington Recognition Memory Test; WASI, Wechsler Abbreviated Scale of Intelligence; MT, Mentalizing Task; BiaJ, Beads in a Jar; MTS, Mental Test Score; DCT, Digit Copying Test; DSST, Digit Symbol Substitution Test; SRB1, Synonym Test; SRB2, Figure Classification Test; SRB3, Block Design Test; PSIF, Identical Forms Test; TPMT, Thurstone Picture Memory Test; MIR, MIR Memory Test; PRT, Prose Recall Test; TWMT, Ten Word Memory Test; JFE, Judgement of Facial Expressions; BFM, Benton test of Facial Matching; RFF, Recognition of Famous Faces; VOSP, Visual Object and Space Perception battery; AHPQ, Annett's Hand Preference Questionnaire; WISC, Wechsler Intelligence Scale for Children; FAB, Frontal Assessment Battery; HVOT, Hooper Visual Organization Test.

Table 2

Overview of longitudinal studies on cognitive functioning in LOS and VLOSP

Author(s)	Participants	Follow-up assessment	Age	Instruments	Treatment context	Findings
Brodaty et al. (2003)	T0: LOS N= 27 Healthy controls N=34 T1 (after 1 year) LOS N=22 Healthy controls N=31 T2 (after 5 years) LOS N=19 Healthy controls N=24	T0: baseline assessment T1: follow-up after 1 year T2: follow-up after 5 years	M: 73.6 SD: 9.7 M: 71.8 SD: 7.4 (cf. Sachdev et al. 1999) M:75.2 SD:7.9 M:70.7 SD:6.8	-CDR -MMSE -CDS	Hospitalized and outpatients	After 5 years the mean MMSE score declined by 6.5 points in LOS, whereas the mean score remained stable in healthy controls. The level of cognitive decline after 5 years as assessed with the CDS and CDR was also worse in LOS compared with healthy controls. Impaired memory function seems common among patients with LOS. However, 9 of the 19 LOS patients (47.4%) developed dementia (5 AD, 1VaD, 3 dementia NOS) after 5 years as opposed to none of the controls.

Holden et al. (1987)	Functional/organic paranoid psychosis with onset after 60 years N=37	T0: baseline assessment T1: follow-up after 10 years	Functional N=24 M:68.5 Range: 60-79 Organic N=13 M:72.5 SD:60-82	-GWQ	Hospitalized at baseline assessment	At follow-up after 10 years, 24 cases appeared to be functional psychosis, whereas 13 were diagnosed as organic psychosis which progressed to dementia. The latter group had significantly lower GWQ scores at baseline assessment. There was nog cognitive follow-up assessment.
Hymas, Naguib & Levy (1989)	LOS N=42 Healthy controls N=23 Cf. Naguib & Levy (1987)	T0: baseline assessment T1: follow-up after 3.7 years	M:75.9 SD:8.6 M:77.9 SD:9	-MTS	Cf. Naguib & Levy (1987)	Both groups showed a significant decline at follow-up, but the decline was greater in LOS subjects. 14 of the 42 subjects were rated as cognitively impaired.
Laks et al. (2006)	LOS N=13	T0: baseline assessment T1: follow-up after 1 year	M:66.08 SD:11.02	-MMSE -CAMCOG	Outpatients	MMSE scores were lower than the average for healthy Brazilian elderly. CAMCOG scores were within the average range. Cognition, as assessed with the MMSE and CAMCOG, remained stable in LOS over the course of one year.
Mazeh et al. (2005)	VLOSP N=21 AOS old	T0: baseline assessment	Older than 70 years, no further specifications	-telephone interviews with the primary caregivers	Hospitalized (AOS, VLOSP) and	13 VLOSP patients appeared cognitively intact at follow-up (minimum 6 months up to 30 months) compared with 16 control subjects.

	N=21	T1: follow-up after 6 to 30 months			outpatients (VLOSP)	
Palmer et al. (2003)	Healthy controls N=56 LOS N=37 AOS N=71 AD with psychosis N=67 AD without psychosis N=72	T0: baseline assessment T1: follow-up after 1 year T2: follow-up after 2 years	M:63.1 SD:9.5 M:63.1 SD:8.4 M:60.4 SD:8.2 M:72.0 SD:7.2 M:72.1 SD:7.4	-MMSE -DRS	Outpatients	There was a stable pattern of performance on the MMSE and DRS at follow-up after 1 and 2 years in the LOS group. This pattern was comparable to that of normal controls and AOS subjects. It was dissimilar to the cognitive decline observed in both AD groups.

Note. CDR, Clinical Dementia Rating scale; MMSE, Mini Mental State Examination; CDS, Cognitive Distortion Scale; GWQ, Gresham Ward Questionnaire; MTS, Mental Test Score; CAMCOG, Cambridge Cognitive assessment battery; DRS, Dementia Rating Scale.

Table 3

Overview of selection criteria with respect to age of onset in LOS and VLOSP

	Age of onset : criterium	Age of onset: M (SD)	Current age: M (SD or range)
LOS (n=7)			
Brichant-Petitjean et al. (2013)	> 45 and < 60	50.88 (9.16)	77.36 (75.5-79.22)
Hanssen et al. (2015)	> 40 and < 60	49.13 (5.54)	58.13 (53.02-63.23)
Heaton et al. (1994)	> 45 and < 60	53.9 (6.1)	59.0 (9.1)
Huang & Zhang (2009)	> 40 and < 60	65.3 (4.7)	66.0 (5.5)
Smeets-Janssen et al. (2013)	> 40 and < 60	46.9 (5.3)	67.3 (5.8)
Vahia et al. (2010)	> 40 and < 60	48.1 (7.3)	57.6 (8.7)
Zakzanis et al. (2001)	> 45 and < 60	48.35 (3.21)	57.84 (8.57)
LOS and VLOSP (n=14)			
Almeida et al. (1995a)	> 55	Not specified	77.36 (75.50-79.22)
Almeida et al. (1995b)	> 55	Not specified	77.36 (75.50-79.22)
Brodaty et al. (2003)	> 50	66.4 (50-87)	73.6 (9.7)
Girard et al. (2011)	> 50	71.00 (5.50)	75.6 (4.00)
Henderson et al. (1998)	Not specified	Not specified	78.9 (6.5)

Hopkins & Roth (1953)	> 60 (1 exception)	Not specified	75.6 (65-86)
Jeste et al. (1995)	> 45	54.7 (7.3)	60.4 (7.6)
Laks et al. (2006)	> 50	59.38 (11.91)	66.08 (11.02)
Miller et al. (1991)	> 45	Not specified	60.1 (10.1)
Palmer et al. (2003)	> 45	Not specified	63.1 (8.4)
Sachdev et al. (1999)	> 50	66.4 (50-87)	73.6 (9.7)
Sachdev et al. (1997)	> 50	Not specified	73.2 (10.6)
Sadek et al. (2012)	> 50	Not specified	72.5 (8.29)
Zakzanis et al. (2003)	> 45 (1 exception > 65)	Not specified	57.84 (8.57)

VLOSP (n=9)

Hanssen et al. (2015)	> 60	72.39 (7.72)	75.68 (72.56-78.80)
Harris et al. (2014)	> 65	80.84 (8.73)	83.47 (6.45)
Holden et al. (1987)	> 60	Not specified	Not specified
Hymas et al. (1989)	> 60	Not specified	Not specified
Mazeh et al. (2005)	> 70	Not specified	72.7 (5.9)
Moore et al. (2006)	> 60	72.38 (6.87)	76.90 (5.99)
Naguib & Levy (1987)	>= 60	Not specified	75.27 (6.29)
Östling et al. (2004)	85	85	85
Phillips et al. (1997)	> 60	75.67 (5.03)	80.33 (5.51)

Table 4

Implications for clinical practice

Implications for differential diagnosis
• Intellectual deterioration is present in LOS and VLOSP, whereas levels of premorbid intelligence are average
• There is diffuse but less severe impairment noticeable in several cognitive domains in LOS and VLOSP compared with normally ageing individuals and AOS
• Consolidation is more preserved than learning in LOS and VLOSP as opposed to AD
• Language is equally impaired in LOS/VLOSP and in AD
• Executive dysfunction in LOS compared with FTD is characterized by deficits in working memory, as opposed to verbal fluency, abstraction and cognitive flexibility