Extended letter to the editor

Hippocampal volume as a vulnerability marker for late onset psychosis: Associations with memory function and childhood trauma

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Hippocampus as vulnerability marker for late onset psychosis

Dear editor,

In a considerable amount of individuals the onset of psychosis is delayed until later in life, even after the age of 60 years. This condition is referred to as very-late-onset schizophrenia-like psychosis (VLOSLP) and it is characterized by paranoid or partition delusions, as well as multimodal hallucinations (Howard et al., 2000). Although a delayed manifestation of psychotic symptoms appears counterintuitive, the life-cycle model of stress provides a well-established theoretical framework to understand associations between early adversity and late-onset psychopathology, suggesting that severe childhood distress causes the hyperactivation and sensitization of the hypothalamus-pituitary-adrenal (HPA) axis stimulating the production of glucocorticoids that exert lasting harmful effects on brain structures regulating stress such as the hippocampus, and hence leading to a lifelong increased vulnerability to the development of psychopathology (Lupien et al., 2009).

In line with this, a recent meta-analysis confirmed dysregulation of the HPA-axis and reduced hippocampal volumes in individuals with early-onset schizophrenia (EOS), many of whom experienced trauma early in life (Ruby et al., 2014). Moreover, childhood trauma has been related to hippocampal volume reductions as well as associated cognitive changes, particularly (verbal) memory impairment in adult survivors (Bremner et al., 1995). In addition, preliminary research demonstrated the presence of early adversity in individuals with VLOSLP and confirmed verbal memory deficits in VLOSLP (Fuchs, 1999; Van Assche et al., 2017). Yet, there are no studies addressing how pathophysiological mechanisms and psychosocial factors interact in its aetiology and phenomenology.

We conducted a cross-sectional study in order to gain insight into the relationships between VLOSLP, hippocampal volume, early adversity and memory function. We compared patients with VLOSLP (n=36; mean age 76.72years, 25% male), consecutively admitted to

our geriatric ward, with late-onset depression (LOD) as a clinical control group (n=34; mean age 76.15years, 32% male), and age and sex matched community dwelling healthy controls (n=36; mean age 75.72years, 25% male). Hippocampal volumes (HV) were derived from manual segmentation of 3T structural MRI data. The Rey Auditory Verbal Learning Test (RAVLT) provided estimates of memory function. The Childhood Trauma Questionnaire-Short Form (CTQ-SF) served as a self-report of childhood abuse and neglect. All participants signed an informed consent and the study was approved by the Ethics Committee of the University Hospitals of Leuven.

Results showed that total HV significantly differs between groups, $F(2, 103)=15.078$, $p < .001$, with larger volumes in healthy controls, and no significant difference between both clinical groups (see Figure 1). As hypothesized, HV was strongly related to memory dysfunction in both clinical groups, with $r(34)=.44$, p 0.008 in VLOSLP and $r(32)=.46$, p 0.007 in LOD, but not in controls, $r(34)=.10$, p 0.554. Moreover, there was a significant difference in self-reported childhood trauma $F(2,79)=6.35$, p 0.003, with the VLOSLP group reporting more trauma (CTQ total $M=37.61$, $SD=10.19$) than the group of individuals with LOD (CTQ total $M=28$, $SD=1.33$) or the controls (CTQ total $M=34.19$, $SD=5.52$). However, HV across or within groups were not clearly related to childhood trauma.

Although there were no significant associations between HV and childhood trauma, a higher self-reported prevalence of childhood trauma in VLOSLP is consistent with prior findings (Stafford et al., 2018). Lack of significance might actually point to the need for larger samples as there was only a subgroup of 82 who completed the CTQ-SF, consisting of 36 individuals with VLOSLP, 36 healthy controls and 10 individuals with LOD. Moreover, previous studies demonstrated that the majority of individuals reporting childhood maltreatment did not go on to develop psychopathology, suggesting that there are protective factors in some individuals with a trauma history, psychosocially or neurobiological (Abajobir

et al., 2017). This coincides with the observation that individuals with VLOSLP as opposed to EOS show better premorbid professional, social and cognitive function (Howard et al., 2000). Hence, the underlying neurobiological vulnerability may initially be less pronounced in VLOSLP, which allows individuals to function normally for the greater part of their adult lives, until the brain is affected by normal or accelerated stress-related aging.

Significant relationships between HV and memory in both clinical groups but not the healthy controls suggest that there is a normal variability in volumes that cannot be associated with memory dysfunction (Lupien et al., 2007). However, when HV reductions have reached a critical or 'threshold' value, additional decreases will affect memory, as was the case in both clinical groups. If memory deficits are the result of structural brain changes rather than merely encompassing psychological 'state' effects, they are expected to remain stable after remission of clinical symptoms. Prior research indeed showed residual memory deficits after remission of depressive symptoms in late life (Gallassi et al., 2006).

Interestingly, the observed impairments appear to have less impact on daily functioning than those associated with neurodegenerative conditions, making them more similar to the 'static' encephalopathies observed in early-onset depression and psychosis (Mazeh et al., 2005). Coincidently, in a substantial subgroup of patients (very) late-onset psychosis was not associated with neurodegenerative conditions (Van Assche et al., 2017). Still, it remains conceivable that suspected non-amyloid pathophysiology (SNAP), and primary age-related tauopathy (PART) in particular, may play a role in the pathophysiology of VLOSLP. Notably, a restricted (limbic) tauopathy with little amyloid deposition and preservation of pyramidal cell numbers in the hippocampus has been observed (Casanova, 2003). Similarly, depressive symptoms have recently been related to tau accumulation in the entorhinal cortex and inferior temporal lobe in cognitively normal older adults by means of tau 18F-AV-1451 PET imaging (Gatchel et al., 2017).

To conclude, lower HV may serve as a vulnerability marker for late-onset psychopathology in general, rather than being predictive of psychosis specifically. Moreover, HV reductions are related to memory dysfunction in clinical groups. Although childhood trauma was more prominent in individuals with VLOSLP, we did not find clear associations between childhood trauma and HV, which may point to a lack of power. It would be useful to replicate and extend current findings in larger samples and using a longitudinal design.

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Figure 1. Normalized hippocampal volumes (HV) in individuals with VLOSLP (*M*=6764, *SD*=995), LOD (*M*=6702, *SD*=921) and controls (*M*=7731, *SD*=816). [a] Statistically significant HV reduction in VLOSLP compared with controls, *t*(70)=-4.16, p=<.001. [b] No statistically significant HV reduction in VLOSLP compared with LOD, *t*(68)=1.08, p=.284. [c] Statistically significant HV reduction in LOD compared with controls, *t*(68)=-5.57, p=<.001.