Evaluation of changes in GCase activity and substrate levels in human brain from PD
Lysosomal enzyme activities in postmortem brain tissue of patients with Lewy Body Diseases
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Research question and background
Lysosomal dysfunction is suggested to play a central role in the pathology of Lewy Body
diseases (LBD), including Parkinson’s disease (PD) and Dementia with Lewy Bodies
(DLB). Genetic associations have been identified between PD and different Lysosomal
Storage disorders, for instance in Gaucher Disease, which is caused by a genetic
deficiency of β-glucocerebrosidase (GCase). However, so far, the activity of lysosomal
enzymes in selectively vulnerable brain regions in PD and DLB has not been
investigated in detail. Our study aims to gain more insight into the activity of lysosomal
enzyme activities in vulnerable brain regions in PD and DLB.

Methods and tissues used
Human postmortem brain tissue of 15 PD patients, 15 DLB patients and 15 age-matched
non-demented controls was obtained from the Netherlands Brain Bank. Enzyme
activities of three lysosomal enzymes - β-hexosaminidase, GCase and cathepsin D - and
one endosomal enzyme - cathepsin E - were measured in the substantia nigra, putamen
and superior frontal cortex using enzyme activity assays. In addition, neuronal loss and
the load of α-synuclein pathology were quantified using a Stereo Investigator system.

Results and conclusion
Our results demonstrate that GCase enzyme activities are decreased in PD patients
compared to controls specifically in the substantia nigra (p= 0.04); an effect that was
more pronounced when comparing the total LBD group to controls (p= 0.03). No
differences were observed between the DLB and PD groups. GCase activities in the SN
were close to being significantly associated with the α-synuclein burden (p= 0.08) and
with disease duration (p= 0.08). In addition to GCase, a trend was found for decreased
cathepsin D activities in the frontal cortex of LBD cases (p= 0.07).
In conclusion, we have found a decrease in GCase activity in the substantia nigra of PD
and LBD cases compared to controls, but not in the other brain regions. These findings
support a role for decreased GCase functioning in synucleinopathies and suggest that
this is associated with disease severity.