Identifying the role and mechanisms of selective vulnerability of a novel projection neuron in frontotemporal dementia and other cognitive disorders

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Name of Fellow

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Institution
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ZonMw

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The Netherlands

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Identifying the role and mechanisms of selective vulnerability of a novel projection neuron in frontotemporal dementia and other cognitive disorders

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Alzheimer's disease & other dementias

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Research Abstract
Von Economo neurons (VENs) are elongated, bipolar layer 5 projection neurons whose functions and connections are unknown. These neurons are topographically restricted to the frontoinsular and anterior cingulate cortex in humans and other highly social, encephalized mammals and exhibit selective vulnerability in the behavioural variant of frontotemporal dementia (bvFTD), autism and schizophrenia. A recent discovery by the applicant has revealed the presence of monoaminergic properties in VENs and a small population of surrounding pyramidal neurons, suggesting a unique role of these neurons in the brain, which could possibly underlie the selective vulnerability in social-emotional diseases.
In this project, we aim to further elucidate the biochemical phenotype of VENs and mechanisms of selective vulnerability in human post-mortem material. We will explore the relationship of the VEN biochemical phenotype to the different pathological forms of bvFTD, and explore the presence of novel lysosomal markers which have been recently linked to bvFTD. In addition, we aim to unravel the protein expression of VENs and related neurons in healthy tissue, which provides an unbiased approach to discover VEN-function in humans. Finally, we will explore alterations in protein expression in VENs and related neurons in bvFTD, autism and schizophrenia and AD. To this end, we will use cutting edge anatomical techniques, such as laser capture microscopy and proteomics in combination with in situ hybridization and immunohistochemistry in well-characterised control and autism, schizophrenia and bvFTD patient post-mortem tissue. This research will advance clinical neuroscience by uncovering of the identity of VENs, clarifying the role and mechanism of selective vulnerability of VENs in bvFTD, and suggesting potential pharmocotherapeutic strategies for patients in whom VENs are affected.

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