

Background: Von Economo neurons (VENs) are large spindle cells located in layer V of the fronto-insular (FI) and anterior cingulate cortex (ACC) of human brain. VENs appear in the 8th month of gestation and proliferate selectively in the right hemisphere. The number of VENs at age 4 is comparable to adult numbers. Their putative function is to relay fast information necessary to ascertain social salience, self-awareness, and physiological state. They are also involved in modulation of the autonomic nervous system that is essential for homeostasis. Recently, the role of VENs and pyramidal neurons in psychiatric illness has been explored in conditions of autism, schizophrenia, bipolar disorder, and frontotemporal dementia. This preliminary report describes the number and location of VENs in ACC and insula of post mortem brains in Prader-Willi syndrome (PWS), a neurodevelopmental disorder.

Methods: The NIH NeuroBioBank provided 20 post mortem brains with PWS. Clinical information on 11 cases included age, gender, genetics, BMI, medical history, psychiatric history, and neuropathology. Areas of interest (ACC and FI) were dissected as a block from the right hemisphere of the brain. Each tissue block was prepared, sectioned, Nissl stained and examined to clarify cytoarchitectural boundaries of regions of interest (Fig 1A). VENs and pyramidal cells were identified and their number, location, morphology, and spatial orientation were documented using stereological methods.

Results: To date, seven brains have been examined, and stereological analysis has been performed on 2 of them. VENs

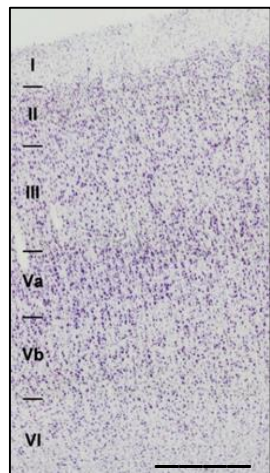


Figure 1A. Cortex micrograph of ACC to identify boundaries of layer V. Scale bar 500 μ m.

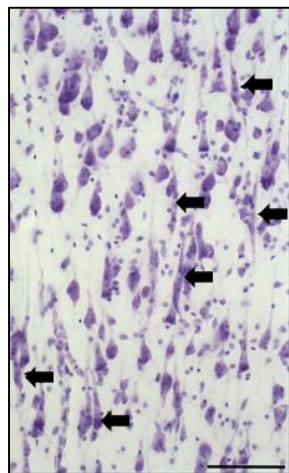


Figure 1B. VENs (black arrows) and pyramidal cells in the ACC. Scale bar 100 μ m.

were more numerous in the ACC around the genu of the corpus callosum in PWS cases compared to ASD and normal controls (Fig 2), and morphology and spatial orientation were normal (Fig 1B). Stereology demonstrated elevated number of VENs with age related decline. Pyramidal cell number did not differ from ASD or controls, and volume was comparable to controls (Fig 3). In PWS there were VENs in the mid and posterior insula, where they are not usually encountered. The functional significance of this is not known, but it appears to be a finding unique to PWS. VENs had oblique spatial orientation, and pyramidal cells were in disarray (Fig 4).

Conclusions: These preliminary results in post mortem brains in PWS have found that VENs in FI and ACC are abnormal in number, distribution, and morphology. The elevated number of VENs in ACC during development may correlate clinically with the onset and expression of the following

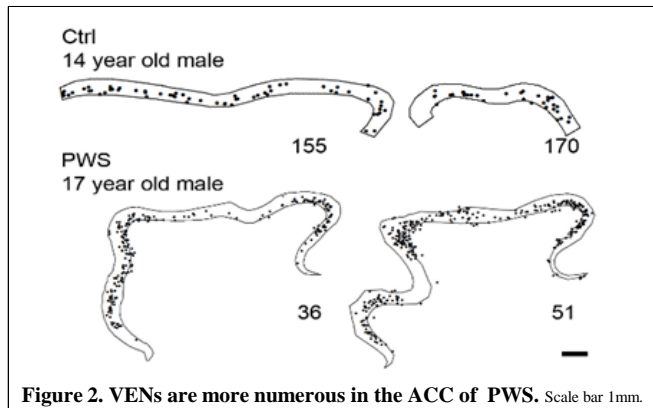


Figure 2. VENs are more numerous in the ACC of PWS. Scale bar 1mm.

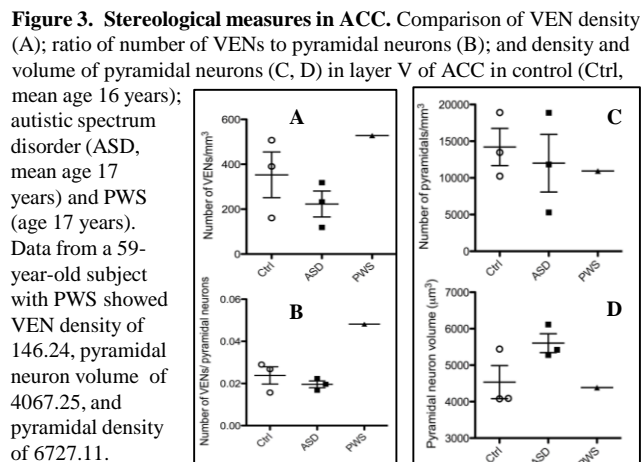
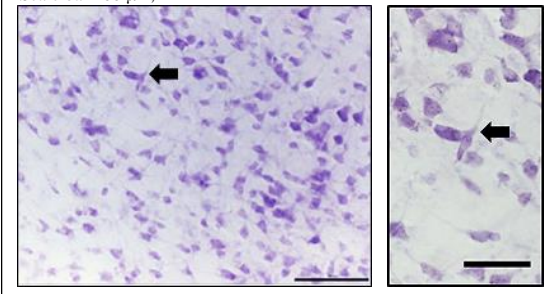


Figure 4. Cellular disarray in the posterior insular cortex. VEN (black arrow) with oblique orientation; enlargement. Scale bar 100 μ m.



aspects of the behavioral phenotype in PWS: heightened reward drive, temper tantrums, and social salience required for both food acquisition and understanding status in the social hierarchy. Stereological data reveals that increased VEN density in PWS may decline with age, and this is consistent with the “mellowing” of behavior (Dykens) and the 4th nutritional stage of satiety (Miller). Pyramidal cell number and volume in ACC of PWS is comparable to controls with slight age-related decline. The spatial orientation and distribution of VENs in FI of PWS is abnormal and comparable to what has been reported in autism spectrum disorder. This may correlate with abnormalities of interoception and autonomic stability. The presence of VENs in the posterior insula appears to be a finding unique to PWS. Because VENs probably differentiated from pyramidal cells, their distribution and orientation may be affected by abnormalities in brain folding during development. Abnormal insular closure has been reported in PWS.

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