FC33: Hilarious Gas for treatment resistant depression in older adults: is it really serious?

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Nitrous oxide (N_2O – also known as Hilarious Gas) has recently emerged has a potential fast-acting antidepressant, based on a number of randomized controlled trials (RCT) in young adults with treatment resistant depression (TRD). The antidepressant mechanisms of N_2O are not fully understood but may include an antagonist action on NDMA receptors, similar to ketamine. N_2O shows additional cerebral effects that may be particularly appropriate for TRD in older adults, including a significant cerebral vasodilatation that facilitates blood brain barrier opening and potentially limits resistance related to poor cerebrovascular functioning. Moreover, N_2O may prove to be particularly well-tolerated in this potentially fragile population, notably because it is not metabolized by the kidney or liver which organs may be impaired with aging.

In this talk, we will be reviewing the available data on the efficacy, safety and pathophysiology of N_2O, with a specific focus on older adults. We will also present results from our group showing a significant reduction in cerebral connectivity in the anterior cingulate cortex (ACC - as measured with pre and post treatment resting state MRI) and large increase in brain tissue pulsations (as measured with Ultrasound) with a successful treatment with N_2O compounds. Finally, perspectives on current studies in older adults from our group (one RCT in non-demented older adults with TRD and one RCT in neurocognitive disorders) will be discussed.

Figure 1 – Changes in ACC connectivity after exposure to N2O compounds

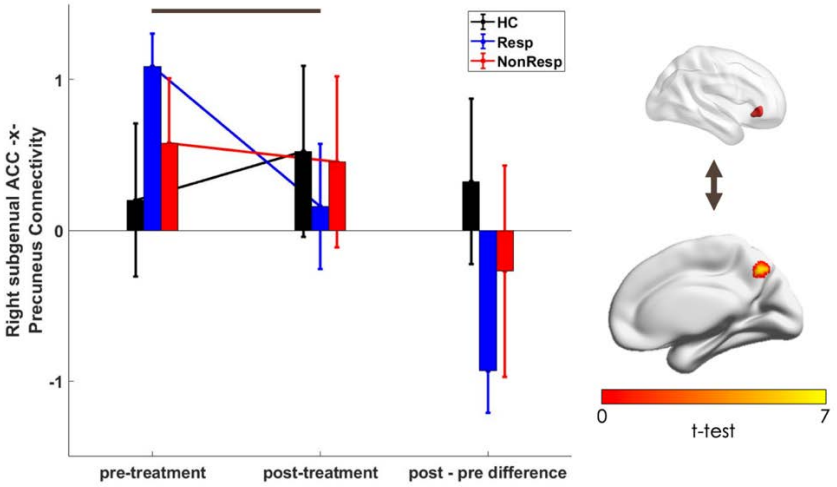

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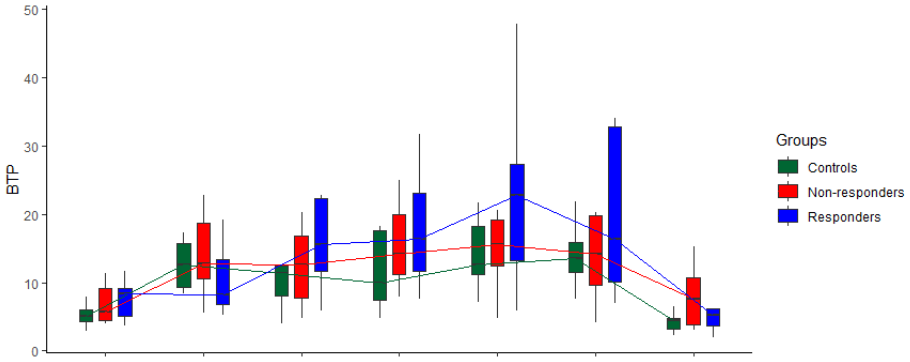
Figure 1 – Changes Brain Tissue Pulsations as assessed with brain ultrasound during N2O exposure



FC34: Cognitive reserve and depressive burden in older adults: variation according to reserve measurement

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Objective: Individual differences in the timing of dementia have been attributed to cognitive reserve (CR), thought to reflect lifelong engagement in stimulating experiences, which provide resilience against brain pathology. In older adults, dementia and depression are closely related, and some studies have linked CR with depression risk in old age. It is unclear if different ways of operationalizing CR exhibit similar association with old-age depression. We examined the association of two measures of CR with depressive burden in older adults: *activity-based CR*, capturing engagement in stimulating activities using proxy variables, and *residual-based* CR, indicating residual variance in cognition, not explained by the brain status.

Methods: We used data on 354 adults aged 60+ from the Swedish National Study on Aging and Care in Kungsholmen, followed for 15 years. Residual-based reserve was computed from a regression predicting episodic memory with a brain-integrity index incorporating six structural neuroimaging markers (white- matter hyperintensities volume, whole-brain gray matter volume, hippocampal volume, lateral ventricular volume, lacunes, and perivascular spaces), age, and sex. Activity-based reserve incorporated education, work complexity, social network, and leisure activities. Depressive burden was captured over the follow- up with the Montgomery-Åsberg Depression Rating Scale and time until clinically relevant level of symptoms (>6) was modelled using Cox proportional hazard models.

Results: Preliminary results indicate that, upon minimal adjustment (age, sex, brain integrity status), top tertiles (ref: bottom tertile) of both *activity-based* (HR: 0.77; 95% CI: 0.61-0.98) and *residual-based* CR (HR: 0.62; 95% CI: 0.44-0.98) were associated with a lower risk of depressive burden onset over 15 years. Upon further adjustment for anthropometrics, health behaviors, and chronic disease burden, the association of activity-based CR was

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