PLATFORM PRESENTATIONS

Adult Neurology (CNS)

A.1

Repurposing Ambroxol as a disease-modifying treatment for Parkinson's disease dementia: A phase 2, randomized, double blind placebo-controlled trial

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Background: Currently there are no disease modifying treatment for Synucleinopathies including Parkinson's disease Dementia (PDD). Carrying a mutation in the *GBA* gene (beta-glucocerebrosidase/ GCAse) is a leading risk factor for synucleinopathies. Raising activity GCAse lowers α-synuclein levels in cells and animal models. Ambroxol is a pharmacological chaperone for GCAse and can raise GCAse levels. Our goal is to test Ambroxol as a disease-modifying treatment in PDD. Methods: We randomized fifty-five individuals with PDD to Ambroxol 1050mg/day, 525mg/day, or placebo for 52 weeks. Primary outcome measures included safety, Alzheimer's disease Assessment Scale-cognitive (ADAS-Cog) subscale and the Clinician's Global Impression of Change (CGIC). Secondary outcomes included pharmacokinetics, cognitive and motor outcomes and and plasma and CSF biomarkers. Results: Ambroxol was well tolerated. There were 7 serious adverse events (SAEs) none deemed related to Ambroxol. GCase activity was increased in white blood cells by ~1.5 fold. There were no differences between groups on primary outcome measures. Patients receiving high dose Ambroxol appeared better on the Neuropsychiatric Inventory. GBA carriers appeared to improve on some cognitive tests. pTau 181 was reduced in CSF. Conclusions: Ambroxol was safe and well-tolerated in PDD. Ambroxol may improve biomarkers and cognitive outcomes in GBA1 mutation carrie.rs Ambroxol improved some biomarkerss. **ClinicalTrials.gov** NCT02914366

A.2

Understanding Grit in healthy older adults at-risk for Alzheimer's disease

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Background: Adherence to healthy lifestyle behaviours or to prescribed medication requires perseverance with stamina, and this is captured by Grit, a non-cognitive trait defined as perseverance and passion for long-term goals. Despite predicting cognitive decline and physical, emotional, and social functioning, Grit remains poorly understood and its neural substrates are unknown in cognitive aging. Methods: Ninety-five cognitively unimpaired older adults with a family history of Alzheimer's disease were recruited through the PREVENT-AD longitudinal cohort. Participants completed tests that assess grit and conscientiousness and underwent resting-state functional magnetic resonance imaging (fMRI). Multivariate pattern analyses (MVPA), a rigorous data-driven whole-brain approach, were used to examine if resting-state functional connectivity of connectome-wide voxels were associated with grit scores, controlling for age, sex, *APOE* ε4 carriership, mean displacement, and conscientiousness. Results: Our analyses identified two large (≥54 voxels) and statistically significant ($p<0.01$ corrected for family-wise error) clusters in the right ventrolateral prefrontal cortex and the left orbitofrontal cortex underlying grit. Conclusions: Being the first to identify functional neural correlates supporting grit in the aging population while accounting for the variance of conscientiousness, our study provides unique insights into the construct which has important applications in adherence to clinical and empirical neurological interventions as well as in successful aging.

A.3

Beta-amyloid is a cytokine and Alzheimer's is an autoimmune disease

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Background: Despite the limited successes of recent amyloid-targetting biologics, the need for a new pathogenesis mechanistic model of Alzheimer's disease (AD) is a continuing priority, to facilitate improved rational drug design. Methods: To devise a new AD model, we performed an extensive, comprehensive series of in silico, in vitro, and in vivo studies explicitly evaluating the atomistic–molecular mechanisms of cytokine-mediated and amyloid-beta (Aβ)-mediated neurotoxicities in AD. Results: A new model of AD has been devised: In response to pathogen-/damage-associated molecular pattern-stimulating events (e.g., infection, trauma, ischaemia), Aβ is released as an early responder cytokine triggering an innate immunity cascade in which Aβ exhibits immunomodulatory/antimicrobial duality. However, Aβ's antimicrobial properties result in a misdirected cytotoxic attack upon "self" neurons, arising from the electrophysiological similarities between neurons and bacteria in terms of transmembrane potential and anionic charges on outer membrane macromolecules. The subsequent breakdown products (amyloid-ganglioside complexes) released from the damaged neurons diffuse to adjacent neurons eliciting further release of Aβ, leading to a chronic, self-perpetuating disease cycle. In short, AD occurs because Aβ cannot differentiate neurons from bacteria. Conclusions: An innovative new model of AD has been devised, recognizing Aβ as a physiologically oligomerizing cytokine and conceptualizing AD as brain-centric autoimmune disorder of innate immunity.