Culturally Sensitive Cognitive Stress Test is Related to Alzheimer's Disease (AD) Signature Regions on MRI

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Background: Dysfunction of the GABA neurotransmission system is one of the most accepted pathophysiologic mechanisms for autism spectrum disorder (ASD). This pilot study aims at demonstrating the GABAA receptor binding potentials and GABA levels in high-functioning adults with ASD are distinctly different from age-matched typically-developing controls (TD).

Methods: Participants were scanned on GE SIGNA simultaneous PET/MR system. [18F]flumazenil was used as radiotracer for the GABAA receptors. During PET data acquisition, MR T1 and T2-weighted structural sequences were acquired. For the MRS measurements of GABA, MEGA-SPECIAL (TE=80ms, TR=2s) was performed on the bilateral thalami. A reference tissue model (Ichise model; MRTM0) was used to calculate binding potentials (BPND) with pons as the reference region. The MEGA-SPECIAL edited spectrum was obtained by subtracting the editing OFF spectrum from the editing ON spectrum. GABA level was estimated from the integrated 3ppm peak area in the edited spectrum divided by the Cre peak area.

Results: Six healthy male volunteers and two adults with ASD were scanned. Highest uptake was observed in the neocortical regions and limbic system, intermediate in the cerebellum, thalami and basal ganglia, and low uptake in the brainstem. Significant differences in BPND were found in the caudate nucleus (1.5 in TD vs. 1.9 in ASD; p=.035) and brainstem (0.4 in TD vs. 0.6 in ASD; p=.043). The mean thalamic GABA/Cre ratio in TD (7.9) is higher than ASD (5.8).

Conclusions: GABAA receptor densities appear to be higher in high-functioning adults with ASD, as compared to TD. Further studies are warranted to confirm this finding.

311. DLPFC Neuroplasticity and Working Memory Performance in Alzheimer's Disease

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Background: Working memory deficits are known in Alzheimer's disease (AD). Dorsolateral prefrontal cortex (DLPFC) plasticity is important for working memory. The aim of this study is to assess DLPFC plasticity in vivo and its relationship to working memory in AD.

Methods: Participants with AD and healthy adults 65 years or older were enrolled. Paired Associative Stimulation (PAS) combined with electroencephalography (EEG) was used to assess DLPFC plasticity. PAS-induced potentiation of cortical evoked activity (CEA) over the DLPFC was used as a measure of plasticity. The N-Back task (1 and 2-back) was used to assess working memory.

Results: 33 participants with AD (female = 17, mean Age = 76.5, SD = 6.2) and 18 healthy adults (female = 10, mean Age = 75.6, SD = 5.5) were enrolled. Participants with AD had impaired potentiation of CEA (mean = 1.18, SD = 0.25) compared to healthy adults (mean = 1.40, SD = 0.34) (Cohen's d = 0.78, p = 0.010). They were also impaired on 1-back (Cohen's d = 1.87, p < 0.001) and 2-back (Cohen's d = 2.55, p < 0.001) performance. Finally, potentiation of CEA was positively correlated with working memory performance on 1-back (Pearson's correlation, r = 0.34, p=0.016) and 2-back (Pearson's correlation, r = 0.42, p=0.004) conditions.

Conclusions: This is the first study showing impaired DLPFC plasticity and its relationship to working memory in patients with AD. These findings could lead to the development of novel biomarkers based on DLPFC plasticity as well as novel treatment targets for AD.

312. Culturally Sensitive Cognitive Stress Test is Related to Alzheimer's Disease (AD) Signature Regions on MRI

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Background: Culturally sensitive cognitive measures able to detect deficits in persons with incipient AD is a priority in the field due to the growing elderly Hispanic population. The Loewenstein-Acevedo Scales of Semantic Interference and Learning (LASSI-L), is a novel assessment with high levels of sensitivity and specificity that has been validated in Spanish. This study aims to relate cognitive performance on the LASSI-L to changes in MRI brain volumes in English-speaking (ES) and Spanish Speaking (SS) older adults.

Methods: We studied 30 ES participants and 21 SS participants diagnosed with amnestic Mild Cognitive Impairment (aMCI) who had both the LASSI-L and MRI brain scans. 43 ES and 20 SS cognitively normal (CN) participants were used as a control. Performance on the LASSI-L indices was compared to brain volumes in regions vulnerable to AD pathology.

Results: LASSI-L Cued B2 recall is associated with volume loss in biologically relevant regions for both ES and SS aMCI participants. The LASSI-L discriminates aMCI from CN participants in both ES and SS groups. ES aMCI participants seem to have more volume loss in the hippocampus than SS MCI patients. While ES aMCI and ES CN can be readily differentiated by MRI, this is not true for the corresponding SS groups.

Conclusions: LASSI-L offers a well-validated and effective memory measurement paradigm that has shown to be a cross-culturally sensitive in diagnosing aMCI and CN Hispanic elderly. The Cued B2 measure is related to brain volumes in AD sensitive regions in both SS and ES with aMCI.
Supported By: R01, P01
Keywords: Alzheimers, MCI, Aging, Spanish, LASSI-L

313. Cortical Surface Based Threshold Free Cluster Enhancement and Cortex-Wise Mediation

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Background: Threshold-free cluster enhancement (TFCE) is a sensitive means to incorporate spatial neighborhood information in neuroimaging studies without using arbitrary thresholds. The majority of methods have applied TFCE to voxel-wise data. The need to understand the relationship among multiple variables and imaging modalities has become critical.
Methods: We propose a new method of applying TFCE to vertex-wise statistical images as well as cortex-wise (either voxel- or vertex-wise) mediation analysis. We present TFCE_mediation that can be used for cortex-wise multiple regression analysis with TFCE, and additionally cortex-wise mediation using TFCE. The toolbox are written using free software packages, and they are publicly available (https://github.com/trislett/TFCE_mediation). We validated TFCE_mediation in healthy controls from two independent multimodal neuroimaging samples (N=199; N=183).
Results: We found a consistent structure-function relationship between surface area and the first independent component (IC1) of the N-back task, that white matter fractional anisotropy is strongly associated with IC1 N-back, and that our voxel-based results are essentially identical to FSL randomise (all PFWE<0.05). Using cortex-wise mediation, we showed that the relationship between white matter FA and IC1 N-back is mediated by surface area in the right superior frontal cortex (PFWE<0.05). We also demonstrated this same mediation model is present using vertex-wise mediation (PFWE<0.05).
Conclusions: Cortex-wise analysis with TFCE provides an effective analysis of multimodal neuroimaging data. Further, cortex-wise mediation analysis may identify or explain a mechanism that underlies an observed relationship among a predictor, intermediary and dependent variables in which one of these variables are assessed at a whole brain scale.
Supported By: CIHR, BMBF, DFG
Keywords: Cortical surface area, Cortical Thickness, Diffusion Tensor Imaging (DTI), Threshold-free Cluster Enhancement (TFCE), Mediation Analysis

314. Hedonic Capacity as a Predictor of ADHD and Treatment Response in Depressed Patients

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Background: Depression has become a major public health concern as rates continue to increase and has become among the leading cause of disability and subsequent death. Research suggests that more than 11% of adolescents experience depression and that depressed adolescents are 6-times more likely to attempt suicide compared to non-depressed individuals. A core symptom of depression, anhedonia, is associated with poorer treatment response in patients treated with traditional antidepressants. Thus, the aim of this study is to determine predictive factors and clinical features associated with the development of treatment-resistant depression (TRD).
Methods: Data is being collected from consecutive referrals to a tertiary-care mood and anxiety clinic 160 subjects have been enrolled in the study to date. Diagnosis was established by using the Mini International Neuropsychiatric Interview Plus 5.0.0 and a semi-structured interview by the treating physician. One-way analysis of variance and t-tests were undertaken to examine predictive factors related to the development of TRD.
Results: Preliminary results suggest that 34% of patients referred for TRD had untreated ADHD of which 48% suffered with chronic anhedonia. The number of failed psychiatric medications (p<0.001), and past SSRI failures (p<0.032) were predictive of ADHD in patients with TRD, with SSRI failure predicting chronic anhedonia (p<0.002).
Conclusions: These results support ADHD as a significant risk factor for the development of TRD, with chronic (trait) anhedonia or low hedonic tone providing a link between TRD and ADHD, which may predict poorer treatment outcomes in a subset of patients treated with SSRIs.
Keywords: Hedonic capacity, Dopamine, Treatment resistance, Depression

315. Retinal Vascular Photography as a Window into the Cardiovascular Burden of Adolescent Bipolar Disorder

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Background: Cardiovascular disease is excessive in bipolar disorder (BD) and occurs up to 17 years prematurely. The cardiovascular burden in BD exceeds what can be explained by traditional cardiovascular risk factors (CVRFs), lifestyle, and/or medications. This study examines retinal vascular photography, a proxy for cerebral microvascular pathology,