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64 Neuroimaging Evidence of Neurodegenerative Disease in Former Professional American Football Players Who "Fail" Validity Testing: A Case Series

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Objective: Former professional American football players have a high relative risk for neurodegenerative diseases like chronic traumatic encephalopathy (CTE). Interpreting low cognitive test scores in this population occasionally is complicated by performance on validity testing. Neuroimaging biomarkers may help inform whether a neurodegenerative disease is present in these situations. We report three cases of retired professional American football players who completed comprehensive neuropsychological testing, but "failed" performance validity tests, and underwent multimodal neuroimaging (structural MRI, Aβ-PET, and tau-PET).
Participants and Methods: Three cases were identified from the Focused Neuroimaging for the Neurodegenerative Disease Chronic Traumatic Encephalopathy (FIND-CTE) study, an ongoing multimodal imaging study of retired National Football League players with complaints of progressive cognitive decline conducted at Boston University and the UCSF Memory and Aging Center. Participants were relatively young (age range 55-65), had 16 or more years of education, and two identified as Black/African American. Raw neuropsychological test scores were converted to demographically-adjusted z-scores. Testing included standalone (Test of Memory Malingering; TOMM) and embedded (reliable digit span, RDS) performance validity measures. Validity cutoffs were TOMM Trial 2 < 45 and RDS < 7. Structural MRIs were interpreted by trained neurologists. Aβ-PET with Florbetapir was used to quantify cortical Aβ deposition as global Centiloids (0 = mean cortical signal for a young, cognitively normal, Aβ negative individual in their 20s, 100 = mean cortical signal for a patient with mild-to-moderate Alzheimer's disease dementia). Tau-PET was performed with MK-6240 and first quantified as standardized uptake value ratio (SUVR) map. The SUVR map was then converted to a w-score map representing signal intensity relative to a sample of demographically-matched healthy controls.
Results: All performed in the average range on a word reading-based estimate of premorbid intellect. Contribution of Alzheimer's disease pathology was ruled out in each case based on Centiloids quantifications < 0. All cases scored below cutoff on TOMM Trial 2 (Case #1=43, Case #2=42, Case #3=19) and Case #3 also scored well below RDS cutoff (2). Each case had multiple cognitive scores below expectations (z < -2.0) most consistently in memory, executive function, processing speed domains. For Case #1, MRI revealed mild atrophy in dorsal fronto-parietal and medial temporal lobe (MTL) regions and mild periventricular white matter disease. Tau-PET showed MTL tau burden modestly elevated relative to controls (regional w-score=0.59, 72nd%ile). For Case #2, MRI revealed cortical atrophy, mild hippocampal atrophy, and a microhemorrhage, with no evidence of meaningful tau-PET signal. For Case #3, MRI showed cortical atrophy and severe white matter disease, and tau-PET revealed significantly elevated MTL tau burden relative to controls (w-score=1.90, 97th%ile) as well as focal high signal in the dorsal frontal lobe (overall frontal region w-score=0.64, 74th%ile).
Conclusions: Low scores on performance validity tests complicate the interpretation of the severity of cognitive deficits, but do not negate the presence of true cognitive impairment or an underlying neurodegenerative disease. In the rapidly developing era of biomarkers, neuroimaging tools can supplement neuropsychological testing to help inform

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whether cognitive or behavioral changes are related to a neurodegenerative disease.

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65 Is Basal Forebrain Volume Loss Associated with Visual Hallucinations, Mild Cognitive Impairment, or Concomitant Symptomology in Advanced Parkinson's Disease?

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Objective: Among individuals with Parkinson's Disease (PD), visual hallucinations (VH) and mild cognitive impairment (MCI) are highly prevalent and often co-occur. Atrophy in similar brain regions [e.g. cholinergic basal forebrain (BF) nuclei] as well as specific cognitive difficulties (e.g. posterior-cortical abilities such as semantic fluency and visuoperception) have been associated with the presentation of each symptom type. While there are separate lines of evidence implicating BF volume in MCI and VH, no study to date has examined BF integrity in patients with concurrent MCI and VH symptomology. Furthermore, no prior studies examining BF integrity in MCI and VH have accounted for the potential confounding effects of dopaminergic medications which are known to exacerbate both symptom types. The aims of this study were to harmonize or bridge the two bodies of literature to determine the common neural substrate of PD-VH and PD-MCI (with an emphasis on the BF), to examine the confounding effects of dopaminergic pharmacotherapy, and to examine whether non-dopaminergic "posterior" cognitive abilities differ between PD-MCI with versus without VH.
Participants and Methods: This study used a clinical chart review and MRI data to examine the associations between BF volume in a large group (n=296) of advanced PD patients (~10 years disease duration) with and without each VH and MCI, covarying the effect of dopaminergic therapy. A two-way ANCOVA was run on total and regional BF volumes (i.e., total BF volume, and four nuclei including Ch4, Ch4p, Ch1-2, Ch3) using VH and MCI as independent variables, while covarying for dopaminergic medication. Using Mann-Whitney U tests, we compared the performance of individuals with MCI-VH versus that of individuals with MCI-noVH on tasks of semantic verbal fluency and of visuoperceptual skills (e.g., judgement of line orientation, object decision, and silhouettes).
Results: There were two major findings: (1) atrophy of the Ch4 region in the BF was associated with MCI with VH while Ch1-2 was associated with MCI regardless of VH status, and (2) patients with both MCI and VH had poorer performance than individuals with MCI without VH on tasks measuring object recognition but not on tasks of visuospatial perception or semantic verbal fluency. These results remained stable regardless of whether or not dopaminergic medication was included in the model.
Conclusions: PD is a heterogeneous disease with different subtypes reflecting both dopaminergic and cholinergic dysfunction. Our findings suggest further dissociations within the cholinergic system. First, atrophy in Ch4, which projects to the cortical mantle, was preferentially associated with VH symptoms and object-based visuoperception deficits. This is consistent with proposals that VH are real-world manifestations of visuoperceptual deficits. Second, Ch1-2 atrophy, which projects primarily to the hippocampus, was associated with MCI regardless of VH. Future research will extend this work to other cognitive abilities such as memory, to analyses of brain networks that implicate the BF, and to the investigation of the relationship between anti-cholinergic medications and symptom presentation in PD.

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