3 Are we Up-Front About Switching or are we Side-Stepping the Issue: Localization of Cognitive Switching Measures with Cortical Thickness

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Objective: Set-shifting/switching tasks, among other measures of executive functioning, are typically thought to represent frontal lobe functioning. However, the neuroanatomical correlates of these tests are not fully established. The aim of this study was to examine associations between individual measures of set-shifting/switching and cortical thickness. We hypothesized that performance on each switching measure would strongly correlate with aggregated cortical thickness within the frontal lobe.
Participants and Methods: Measures of interest included set-shifting subtests of the Delis-Kaplan Executive Function System (DKEFS): Color-Word Inhibition Switching, Category Switching, and Trail Making Test Number-Letter Switching. Archival data from an outpatient memory disorders clinic were reviewed to identify individuals whose neuropsychological evaluations included the measures of interest and had quality-assessed, volumetric MRI data available (n=243; 53.1% male, 81.9% Caucasian, M_{age}=72.4, SD_{age}=6.7). Cortical thickness values were generated by FreeSurfer and averages were calculated for both frontal and temporal lobes, separately. Using partial correlations, controlling for age, we explored associations between each switching trial separately with right and left, frontal and temporal cortical thickness. The strength of associations within each lobe were then compared using Fisher's *r*-to-*z* transformations.
Results: Category Switching was significantly correlated with left and right hemisphere temporal thickness (*r*=0.38 and 0.31, respectively), but was not significantly correlated with left or right frontal lobe cortical thickness (*r*=.12 and .07, respectively). Fisher's *r*-to-*z* transformations revealed significantly stronger relationships between Category Switching and temporal thickness, rather than frontal thicknesses. Trails Switching was also significantly correlated with left and right temporal cortical thickness (*r*=-0.28, and =-0.23, respectively) and bore weaker associations with frontal cortical thickness (*r*=-.13 and *r* = -.14 for left and right hemispheres, respectively). In contrast, Color-Word Inhibition-Switching did not show a significant relationship with frontal or temporal cortical thickness.
Conclusions: Contrary to our hypothesis, stronger associations were observed with temporal lobe cortical thickness for Category Switching. Category Switching involves a language production component which could explain the strong association with temporal cortical thickness compared to frontal cortical thickness. Additionally, the pattern of associations between Trails Switching and frontal and temporal thickness was non-specific. Perhaps most striking is the lack of association between each switching measure and frontal cortical thickness, which was unexpected, given that these measures are used to assess executive functioning, broadly localized to the frontal lobe. Future directions involve examining the associations of these measure with subcortical structures and replicating these findings in larger datasets.

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4 Risk Factor and Biomarker Correlates of FLAIR White Matter Hyperintensities in Former American Football Players

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Objective: White matter hyperintensity (WMH) burden is greater, has a frontal-temporal distribution, and is associated with proxies of exposure to repetitive head impacts (RHI) in former American football players. These findings suggest that in the context of RHI, WMH might have unique etiologies that extend beyond those of vascular risk factors and normal aging processes. The objective of this study was to evaluate the correlates of WMH in former elite American football players. We examined markers of amyloid, tau, neurodegeneration, inflammation, axonal injury, and vascular health and their relationships to WMH. A group of age-matched asymptomatic men without a history of RHI was included to determine the specificity of the relationships observed in the former football players.
Participants and Methods: 240 male participants aged 45-74 (60 unexposed asymptomatic men, 60 male former college football players, 120 male former professional football players) underwent semi-structured clinical interviews, magnetic resonance imaging (structural T1, T2 FLAIR, and diffusion tensor imaging), and lumbar puncture to collect cerebrospinal fluid (CSF) biomarkers as part of the DIAGNOSE CTE Research Project. Total WMH lesion volumes (TLV) were estimated using the Lesion Prediction Algorithm from the Lesion Segmentation Toolbox. Structural equation modeling, using Full-Information Maximum Likelihood (FIML) to account for missing values, examined the associations between log-TLV and the following variables: total cortical thickness, whole-brain average fractional anisotropy (FA), CSF amyloid β_{42}, CSF p-tau$_{181}$, CSF sTREM2 (a marker of microglial activation), CSF neurofilament light (NfL), and the modified Framingham stroke risk profile (rFSRP). Covariates included age, race, education, *APOE ε4* carrier status, and evaluation site. Bootstrapped 95% confidence intervals assessed statistical significance. Models were performed separately for football players (college and professional players pooled; n=180) and the unexposed men (n=60). Due to differences in sample size, estimates were compared and were considered different if the percent change in the estimates exceeded 10%.
Results: In the former football players (mean age=57.2, 34% Black, 29% *APOE ε4* carrier), reduced cortical thickness (B=-0.25, 95% CI [-0.45, -0.08]), lower average FA (B=-0.27, 95% CI [-0.41, -.12]), higher p-tau$_{181}$ (B=0.17, 95% CI [0.02, 0.43]), and higher rFSRP score (B=0.27, 95% CI [0.08, 0.42]) were associated with greater log-TLV. Compared to the unexposed men, substantial differences in estimates were observed for rFSRP ($B_{control}$=0.02, $B_{football}$=0.27, 994% difference), average FA ($B_{control}$=-0.03, $B_{football}$=-0.27, 802% difference), and p-tau$_{181}$ ($B_{control}$=-0.31, $B_{football}$=0.17, -155% difference). In the former football players, rFSRP showed a stronger positive association and average FA showed a stronger negative association with WMH compared to unexposed men. The effect of WMH on cortical thickness was similar between the two groups ($B_{control}$=-0.27, $B_{football}$=-0.25, 7% difference).
Conclusions: These results suggest that the risk factor and biological correlates of WMH differ between former American football players and asymptomatic individuals unexposed to RHI. In addition to vascular risk factors, white matter integrity on DTI showed a stronger relationship with WMH burden in the former

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football players. FLAIR WMH serves as a promising measure to further investigate the late multifactorial pathologies of RHI.

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5 Associations Between Regional Perfusion and Locus Coeruleus MRI Contrast are Moderated by Plasma Alzheimer's Disease Biomarkers in Older Adults

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Objective: The locus coeruleus (LC) innervates the cerebrovasculature and plays a crucial role in optimal regulation of cerebral blood flow. However, no human studies to date have examined links between these systems with widely available neuroimaging methods. We quantified associations between LC structural integrity and regional cortical perfusion and probed whether varying levels of plasma Alzheimer's disease (AD) biomarkers (Aβ42/40 ratio and ptau181) moderated these relationships.
Participants and Methods: 64 dementia-free community-dwelling older adults (ages 55-87) recruited across two studies underwent structural and functional neuroimaging on the same MRI scanner. 3D-pCASL MRI measured regional cerebral blood flow in limbic and frontal cortical regions, while T1-FSE MRI quantified rostral LC-MRI contrast, a well-established proxy measure of LC structural integrity. A subset of participants underwent fasting blood draw to measure plasma AD biomarker concentrations (Aβ42/40 ratio and ptau181). Multiple linear regression models examined associations between perfusion and LC integrity, with rostral LC-MRI contrast as predictor, regional CBF as outcome, and age and study as covariates. Moderation analyses included additional terms for plasma AD biomarker concentration and plasma x LC interaction.
Results: Greater rostral LC-MRI contrast was linked to lower regional perfusion in limbic regions, such as the amygdala (β = -0.25, p = 0.049) and entorhinal cortex (β = -0.20, p = 0.042), but was linked to higher regional perfusion in frontal cortical regions, such as the lateral (β = 0.28, p = 0.003) and medial (β = 0.24, p = 0.05) orbitofrontal (OFC) cortices. Plasma amyloid levels moderated the relationship between rostral LC and amygdala CBF (Aβ42/40 ratio x rostral LC interaction term β = -0.31, p = 0.021), such that as plasma Aβ42/40 ratio decreased (i.e., greater pathology), the strength of the negative relationship between rostral LC integrity and amygdala perfusion decreased. Plasma ptau181levels moderated the relationship between rostral LC and entorhinal CBF (ptau181 x rostral LC interaction term β = 0.64, p = 0.001), such that as ptau181 increased (i.e., greater pathology), the strength of the negative relationship between rostral LC integrity and entorhinal perfusion decreased. For frontal cortical regions, ptau181 levels moderated the relationship between rostral LC and lateral OFC perfusion (ptau181 x rostral LC interaction term β = -0.54, p = .004), as well as between rostral LC and medial OFC perfusion (ptau181 x rostral LC interaction term β = -0.53, p = .005), such that as ptau181 increased (i.e., greater pathology), the strength of the positive relationship between rostral LC integrity and frontal perfusion decreased.
Conclusions: LC integrity is linked to regional cortical perfusion in non-demented older adults, and these relationships are moderated by plasma AD biomarker concentrations. Variable directionality of the associations between the LC and frontal versus limbic perfusion, as well as the differential moderating effects of plasma AD biomarkers, may signify a compensatory mechanism and a shifting pattern of hyperemia in the presence of aggregating AD pathology. Linking LC integrity and cerebrovascular regulation may represent an important understudied pathway of dementia risk and may

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