Plasma BDNF associations with cortical thickness in normal controls and subjects mild cognitive impairment

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Background: The search for reliable prognostic and diagnostic biomarkers for Alzheimer’s disease (AD) has recently intensified. Peripheral blood biomarkers can be useful in finding those most at risk for developing the disease. The interaction between protein and neuroimaging biomarkers can help us better understand the disease pathology.

Methods: We collected peripheral blood and 3D MP-RAGE T1-weighted MRI data in 27 normal controls (NC) and 19 subjects with mild cognitive impairment (Table 1). MCI was diagnosed according to Peterson criteria.

Results: Plasma levels of BDNF showed positive associations with cortical thickness in the bilateral temporo-occipital, dorsal anterior cingulate, left inferior and lateral temporal, left supramarginal and right middle and inferior frontal cortices (left hemisphere \(p_{\text{corrected}}=0.03\); right hemisphere \(p_{\text{corrected}}=0.06\)). We did not find significant associations between cortical thickness and plasma concentrations of ApoE, ApoJ, HSP40, IL6, and TNFα.

Conclusions: Decreased plasma levels of BDNF, a protein known to stimulate neuronal growth and facilitate cortical plasticity, showed significant association with cortical atrophy in the predementia cognitive spectrum. This suggests a potential role of plasma levels of BDNF for predementia diagnostic ascertainment and as a surrogate marker for treatments already in trials that increase BDNF, notably exercise.

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Blood samples were collected in EDTA tubes and centrifuged at 1200 g for 15 minutes. Plasma was aliquoted to nalgene tubes and stored at -80 °C. Plasma concentration of analytes were measured using commercial enzyme-linked immunosorbent assays: apolipoprotein J (ApoJ; Alpco, Salem, NH), brain-derived neurotrophic factor (BDNF; Millipore, Billerica MA), heat shock protein 40 (HSP40, Kamiya Biomedical, Seattle, WA), interleukin 6 (IL6; eBioscience, San Diego, CA), and tumor-necrosis factor α (TNFα; eBioscience, San Diego, CA). Apolipoprotein E (ApoE) was assayed using a previously described ELISA protocol (Sullivan et al., Neurobiol Aging 2009: July 3).

Scans were registered with a 9-parameter transformation to the ICBM53 template and bias-field corrected for spatial and intensity normalization. The brains were automatically skull-stripped with Brainsuite and all volumes were manually edited for mislabeled brain and nonbrain regions. After 3D hemispheric reconstruction 38 sulci per hemisphere were traced and averaged across subjects. The cortical surfaces were parameterized, flattened and warped to align all subjects to a respective average sulcal representation. Three tissue classes (WM, GM, and CSF) were segmented with Brainsuite’s partial volume classifier and resampled to a 0.33 mm isotropic voxel resolution.

The 2D distance (thickness) measured from the CSF/GM and GM/WM boundaries was smoothed with a surface-based kernel of 10 mm and mapped onto the corresponding cortical hemispheric spatial model (Figure 1).

We used linear regression models while adjusting for age and gender to investigate the associations between cortical thickness and plasma levels of ApoE, ApoJ, BDNF, HSP40, IL6, and TNFα. Significance and beta coefficient maps were created (Figure 2). The age- and gender-adjusted maps were corrected for multiple comparisons with permutation analysis at a threshold \(p<0.01\).

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