

Brain-derived Neurotrophic Factor (BDNF) Genotype is Associated with Frontal Gray and White Matter Volume Recovery in Abstinent Alcohol Dependent Individuals

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Introduction:

Single-nucleotide-polymorphisms (SNPs) in genes coding for brain-derived neurotrophic factor (BDNF) catechol-o-methyltransferase (COMT) and dopamine receptor D2 (DRD2) are reported to influence neurobiology and neurocognition in healthy controls. Specifically, the BDNF Val166Met has been shown to influence neurocognition and hippocampal NAA (N-acetylaspartate), the Val158Met SNP of catechol-o-methyltransferase (COMT) has been reported to be associated with smaller temporal and hippocampal volumes and the DRD2 C975 is related to DA2 subcortical receptor binding potential and impulsivity. However, research assessing the influence of these and other genes in brain morphology of those with alcohol use disorders (AUDs) is limited, with no studies assessing the influence of these SNPs on longitudinal changes in brain morphology in the early phase of abstinence. In this preliminary report, we investigated the effects of the aforementioned genotypes on lobar volumes changes over approximately 1 month of abstinence in participants in treatment treatment for AUDs.

Methods:

Forty-four and 65 alcohol dependent individuals (age:51 years) were scanned at 6 ± 3.0 days and 36 ± 7 days respectively after initiation of abstinence from alcohol, on a 1.5 Tesla magnet system (Vision, Siemens Medical Systems, Iselin NJ). The imaging pulse sequences used were: 1) a double spin-echo proton density and T2-weighted oblique-axial imaging (TR/TE₁/TE₂ = 2500/20/80 ms, $1 \times 1 \text{ mm}^2$ in-plane resolution, 3 mm slice thickness) and 2) T1-weighted imaging using a Magnetization Prepared Rapid Acquisition Gradient Echo sequence (TR/TI/TE = 9/300/4 ms, $1 \times 1 \text{ mm}^2$ in-plane resolution, 1.5 mm slabs) oriented orthogonal to the long axis of the hippocampus.. An ABI 7500 real time PCR instrument was used to conduct 5'-nuclease (TaqMan) assays of SNPs of the following genes: COMT (rs4680), DRD2 (rs6277), and BDNF (rs6265). The expectation maximization tissue segmentation method (proposed by Leemput) was applied to the T₁-weighted images to assign a set of probabilities of WM, GM, or cerebrospinal fluid to each MRI voxel. The major lobes and subcortical regions were then parcellated by overlaying the tissue maps on a T1 template. Statistics used a linear mixed model to assess the effects of genotypes of BDNF, DRD2 and COMT on longitudinal changes in frontal, parietal and temporal gray and white matter (i.e., fGM, pGM, tGM, fWM, pWM and tWM respectively). Participant smoking status, age and intracranial volume were used as covariates in all models.

Results:

There was a significant time-by-BDNF interaction for fGM ($F = 4.5$, $p = 0.041$) and a trend for pGM ($F = 3.11$, $p = 0.086$). Valine homozygotes (33% of sample) showed greater volume increases between the two time points (from $215.38 \pm 1.90 \text{ ml}$ to $217.24 \pm 1.88 \text{ ml}$ (mean \pm standard error)) than their heterozygous counterparts (67% of sample) (from $216.29 \pm 2.83 \text{ ml}$ to $216.59 \pm 2.79 \text{ ml}$). There was no time-by-DRD2 or time-by-COMT interaction for any tissue category. None of the other SNPs had an influence on the recovery on regional tissue volumes. Furthermore, intra-cranial volume was not related to any of these SNPs.

Discussion:

BDNF, DRD2 and COMT genes have been implicated in the development and/or maintenance of addictive disorders. This preliminary study examined the influence of specific SNPs on the recovery of brain lobar tissue volumes. Of the three specific SNPs, we observed that only BDNF (rs6265) predicted frontal gray and white matter recovery in abstinent alcohol dependent individuals over four weeks. BDNF facilitates and supports neuronal growth; therefore its associations with brain tissue recovery may indicate cell genesis or increases in neuronal viability. However, our sample size was relatively small; therefore, it is possible that with larger samples associations between brain recovery and DRD2 or COMT exist. Our finding of the influence of BDNF on brain tissue recovery suggests some genetic variability in brain tissue recovery in abstinent alcoholics, suggesting the importance of genotype in the efficiency of volume recovery during abstinence from alcohol.

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