Multimodal imaging of a tescalcin (TESC)-regulating polymorphism (rs7294919) – specific effects on hippocampal gray matter structure

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In two large genome-wide association studies (GWAS) an intergenic SNP (rs7294919) involved in TESC gene regulation has been associated with hippocampus volume. Further characterization of neurobiological effects of the TESC gene is warranted employing multimodal brain-wide structural and functional imaging. Voxel-based morphometry (VBM8) was used in two large, well-characterized samples of healthy individuals of West-European ancestry (Münster sample, N=503; SHIP-TREND, N=721) to analyze associations between rs7294919 and local gray matter volume. In subsamples, white matter fiber structure was investigated using DTI and limbic responsiveness was measured by means of fMRI during facial emotion processing (N=220 and N=264, respectively). Furthermore, gene x environment interaction and gene x gene interaction with SNPs from genes previously found to be associated with hippocampal size (FKBP5, Reelin, IL6, TNF-α, BDNF, 5-HTTLPR/rs25531) were explored. We demonstrated highly significant effects of rs7294919 on hippocampal gray matter volumes in both samples. In wholebrain analyses, no other brain areas except the hippocampal formation and adjacent temporal structures were associated with rs7294919. There were no genotype effects on DTI and fMRI results, including functional connectivity measuress. No GxE interaction with childhood maltreatment was found in both samples. However, an interaction between rs7294919 and rs2299403 in the Reelin gene was found that withstood correction for multiple comparisons. We conclude that rs7294919 exerts highly robust and regionally specific effects on hippocampal gray matter structures, but not on other neuropsychiatrically relevant imaging markers. The biological interaction between TESC and RELN pointing to a neurodevelopmental origin of the observed findings warrants further mechanistic investigations.

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