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ENIGMA Addiction: Neuroimaging Biotypes Supported by Gene Enrichment Analysis

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It is not known whether the inter-individual heterogeneity present in substance use disorders clusters into meaningful subtypes with important differences in etiology and treatment perspectives. Here, we performed cortical thickness based sub-typing on 1,206 alcohol dependent individuals and compared the subtypes with 946 non-dependence controls from the ENIGMA-Addiction working group. Two subtypes were identified by K-means clustering after using principal components analysis to remove variability which our previous work has shown represents a common pattern of psychiatric disease burden. The Silhouette Coefficient and Adjusted Rand Index were used to determine the optimal number of clusters. While Subtype 1 was associated with widespread lower cortical thickness relative to controls, Subtype 2 exhibited higher cortical thickness in the ventral and medial parts of the frontal cortex. Lower subcortical volume than controls characterized both subtypes but was significantly greater in Subtype 2. Support vector machine classifiers built to identify each subtype showed that classification models were substantially improved by including subtype information. This effect was replicated in an independent dataset (dependent, n=279; controls, n=279). The two imaging subtypes were correlated spatially with transcriptional profiles from the Allen Human Brain Atlas. A modified gene set enrichment analysis revealed differential gene expression between the subtypes and controls was significantly enriched for molecular functions related to transmembrane transporter activity and protein binding as well as differentially enriched for astrocytes and endothelial and other brain cell types. The common and distinct molecular manifestations for the two subtypes potentially reflect different neurobiological vulnerabilities to prolonged alcohol exposure.