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Gene by Disease Interaction on Orbitofrontal Gray Matter in Cocaine Addiction

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Introduction: Chronic cocaine use has been associated with structural deficits in brain regions having dopamine receptive neurons. However, the concomitant use of other drugs and common genetic variability in monoamine regulation present additional structural variability. We therefore examined variations in gray matter volume (GMV) as a function of lifetime drug use and the monoamine oxidase A (MAOA) genotype in cocaine use disorders (CUD) and healthy controls.

Methods: We compared 40 men with CUD with 42 male controls scanned with magnetic resonance imaging to assess GMV with voxel-based-morphometry. All individuals were genotyped for the functional polymorphism in the promoter region of the MAOA gene with "high" and "low" alleles. The impact of cocaine addiction on GMV was tested by 1) comparing CUD with controls, 2) testing diagnosis-by-MAOA interactions, and 3) correlating GMV with lifetime cocaine and alcohol use and testing their contribution to GMV beyond other factors. These analyses were conducted in SPM5 with a threshold of $p<.05$, False Discovery Rate corrected and with extracted volumes from the main effect results.

Results: **1)** Individuals with CUD had reductions in GMV in the orbitofrontal (OFC), dorsolateral prefrontal (DLPFC) and temporal cortex, and hippocampus, compared to controls ($F_{1,72}$ ranging from 5.3 - 27.5, p=.05-.0001). **2)** The OFC reductions were uniquely driven by CUD with the low MAOA genotype ($F_{1,68}>5.2$, $p<.005$) and by lifetime cocaine use ($r = -.44$, $p<.005$). **3)** GMV in the DLPFC was driven by lifetime cocaine and alcohol use; in the hippocampus, GMV was driven by lifetime alcohol use ($r = -.46$ and .41, respectively, $p<.005$). These findings were confirmed by multiple regression analysis where the contribution to GMV of demographic, MAOA genotype, and drug use variables were assessed. The resulting R^2 ranged from .36 - .55, indicating that a combination of factors can explain nearly half of the variability in GMV in CUD and that lifetime cocaine and alcohol use are chief contributors to the GM decrements.

Discussion: The regions found to have reduced GMV in CUD in the current study are associated with drug craving and drug seeking behaviors. Since the OFC and hippocampus, in concert with DLPFC regions, have an important executive role in inhibiting previously acquired drug reward mechanisms, these GMV decrements may perpetuate the Impaired Response Inhibition Salience Attribution (I-RISA) syndrome in drug addiction.

We report for the first time, the enhanced sensitivity of CUD low MAOA carriers to GM loss, specifically in the OFC. This gene-by-disease interaction indicates that CUD-L show exacerbated effects of cocaine in the OFC, a region central to reward attribution and to self-control (i.e., I-RISA). The mechanisms by which the MAOA low allele interacts with cocaine use to selectively diminish OFC in the current study remains unknown. The modulating effect of the MAOA genotype on structural variability may have started during early brain development and continuing its impact at adolescence at onset of the disease process. Interestingly, CUD-L in this study had a slightly younger age of onset for cocaine use. It is possible that these particular

individuals who later developed CUD had reduced GMV in the OFC before disease onset, since developmental factors such as maternal smoking are associated with increased likelihood of drug experimentation and decreased thickness of the OFC in adolescence. In this context, it is noteworthy that MAOA-L genotype was associated with risk for alcoholism and antisocial alcoholism.

Lifetime alcohol use was the major contributor of GMV deficit in the DLPFC, temporal cortex and hippocampus of CUD, contributing unique variability to GMV above and beyond the MAOA polymorphism and any of the other factors tested and more so than cocaine use. Animal models of binge alcohol administration support a direct link between high levels of alcohol consumption and neurotoxicity in the hippocampus during adolescence. Similarly, reduced hippocampus volume was found among adolescents with alcohol use disorders. Gray matter loss in the hippocampus may lead to enhanced drug seeking and more self-administration, further facilitating a vicious cycle of cocaine use.

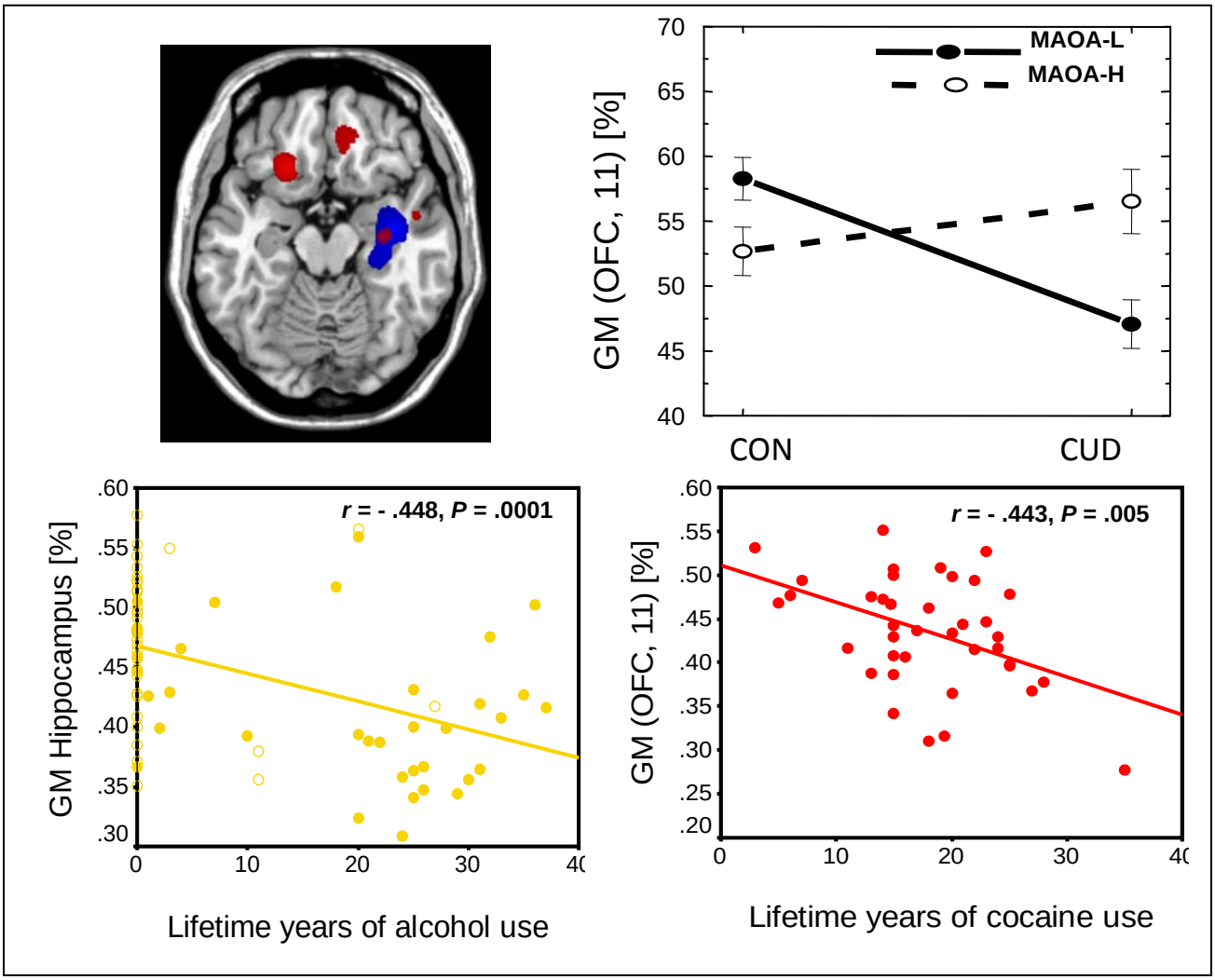

Figure 1. Gene-by-disease interaction in the OFC and correlations with lifetime drug use. Top left: The GMV measures in CUD-L<CON-L (red) and CUD-H<CON-H (blue) is overlaid on the SPM5 canonical template. Right: The respective interaction graph shows regional GMV differences between the groups where CUD-L have the least GM than CUD-H and both CON groups. Error bars represent standard error. Bottom left and right: The respective scatterplots show correlations of GMV (y-axis) and lifetime years of cocaine in the CUD group (red) and lifetime years of alcohol (yellow) in all subjects (the open circles are controls).