613. Shared Inhibitory Dysregulation and Possible Remediation in Intermittent Explosive Disorder and Cocaine Addiction

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Background: Intermittent explosive disorder (IED) is an understudied impulse control disorder marked by episodic reactive aggression. Using an event-related color-word Stroop task during functional MRI (fMRI), we investigated whether IED participants have poor prefrontal cortical (PFC)-mediated error-related processing. We further investigated whether such PFC deficits in IED (A) parallel those seen in cocaine use disorder (CUD), similarly characterized by dysfunctional PFC circuitry; and (B) could be fortified with the indirect dopamine agonist methylphenidate (preliminary follow-up study, new participants).

Methods: We first compared 11 IED, 21 CUD, and 17 controls on Stroop error>correct fMRI activity. Subsequently, in a double-blind placebo-controlled design, we administered oral methylphenidate (20 mg) during fMRI Stroop in 4 IED and 4 controls. We extracted and analyzed the fMRI signal from the same regions showing group differences in the main sample.

Results: In our main sample, IED (and CUD) had error>correct hyperactivations in the anterior cingulate cortex and dorsolateral prefrontal cortex relative to controls (whole-brain SPM8 analyses, p<0.05 corrected). In our preliminary sample, inspection of the extracted fMRI signal means indicated that methylphenidate decreased hyperactivations in these same regions in IED, consistent with our previous study of methylphenidate in CUD.

Conclusions: IED and CUD had comparably hyperactive neural response to errors, suggesting a common neural endophenotype of compromised self-control across psychopathologies. Because methylphenidate reduces aggression in youth and modulates PFC-mediated inefficiencies in multiple self-control disorders, this medication merits further investigation in adult IED.

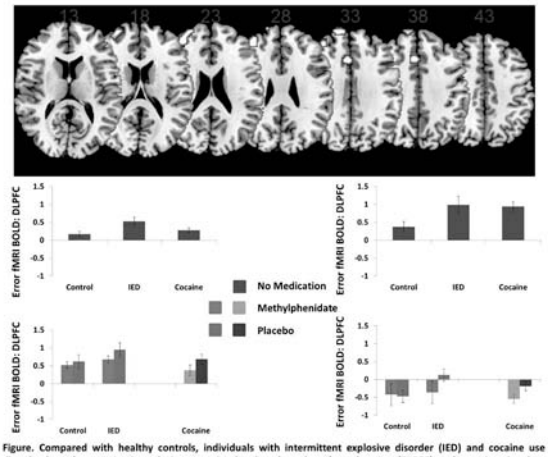

Figure. Compared with healthy controls, individuals with intermittent explosive disorder (IED) and cocaine use disorder have hyperactivations during error in the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), regions that are modulated by methylphenidate during error in these psychopathologies (IED data: current study; cocaine data: from Moeller et al., 2012, Cerebral Cortex).

Keywords: intermittent explosive disorder, cocaine addiction, fMRI, endophenotype, methylphenidate

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614. Genome-wide Expression Profiling Reveals that the Glucocorticoid Receptor Signaling Pathway in Blood and Brain is Associated with Trauma-related Individual Differences

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Background: Identification of convergent signaling pathways associated with trauma-related individual differences is essential for understanding PTSD neurobiology and can pave the design for novel treatments. In the present study, we used a unique and well-validated animal model of PTSD individual differences.

Methods: Sprague-Dawley rats were exposed to predator-scent-stress (PSS) and, 7-days after, tested for anxiety and arousal levels. Rats responded heterogeneously to the stressor and, with the use of cut-off behavioral criteria, we identified rats displaying a PTSD-like syndrome (~25%) and those completely recovered (~25%), with unexposed rats as controls. In tissue obtained 24-h later, genome-wide expression profiling was evaluated using bead DNA-microarrays [p<.050, FDR<5%, ABS(log2RATIO)<0.3] in two limbic stress-regulatory limbic brain-regions (amygdala and hippocampus) and blood. A qPCR validation with the use of additional independent samples was performed (R>0.8, p<.0001).

Results: In the individual gene level, the existence of a small but statistically significant between-tissue overlap (4-21%) underlying trauma-related individual differences, demonstrated the existence of tissue-specific but also across-tissue gene expression in both genders. To uncover convergent across-tissue pathways we statistically predicted the upstream activated/de-activated transcription-factors for each tissue and identified the respective signaling-pathways. Glucocorticoid-receptor (GR) signaling was the only pathway present across-tissue associated with individual differences above the most stringent statistical threshold (p<1.00E-09). The GR involvement in the behavioral response to PSS was confirmed in a follow-up study where ip-corticosterone, 1-h after PSS, prevented primarily anxiety [F(1 24)=6.2 p=.020 and F(1 23)=4.9 p=.003, for males and females, respectively] and, at a trend-level, hyperarousal [F(1 24)=3.3 p=.080 and F(1 23)=4.1 p=.052 for males and females, respectively] 7-days later.

Conclusions: GR-regulated gene expression underlies trauma-related individual differences.

Keywords: PTSD, rat, individual differences, Genome-wide expression, glucocorticoid receptor

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