Discovery of Adversity-Driven, Cue-Vulnerable Phenotype May Enable Brain-Targeted Interventions to Prevent Addiction Relapse

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Rationale: Cocaine-use disorders remain a significant public health problem, with recent fentanyl contamination of the cocaine supply adding a new layer of lethality to the 30-year epidemic. Despite the long-standing problem, there are still no FDA-approved medications for cocaine-use disorders. Part of the difficulty with demonstrating medication effects in prior trials may be related to *heterogeneity* of medication response: some individuals respond, others don't – yielding an averaged response of "no difference from placebo". A potentially important source of heterogeneity in medication response is *prior adversity*: up to two-thirds of individuals with addiction have experienced prior adversity (e.g., emotional, physical or sexual abuse). Based on prior literature, we hypothesized that cocaine patients with a prior history of adversity would evidence (relapse-relevant) *functional* and *structural* brain differences, as compared to individuals without this history. Establishing an "adversity-driven" endophenotype would provide a critical empirical foundation for personalized therapeutics, targeting these brain vulnerabilities.

Methods: *Functional imaging*: Six cohorts of treatment-seeking cocaine patients (total n=73; average age, 44.4; average cocaine use, 17.2 years) participated in a series of BOLD fMRI tasks, including the passive viewing of brief (500ms) evocative (cocaine, aversive, sexual) and comparator (neutral) cues. We tested (SPM 12 pipeline) whether cocaine patients with prior adversity (vs. those without prior adversity) would have greater reactivity to the evocative (vs. neutral) cues in relapse-relevant regions. *Structural imaging*: All participants underwent a high-resolution structural scan (MPRAGE), with optimized voxel-based morphometry (VBM) used for group comparisons. Two cohorts of non-drug users were also added as comparison groups. We tested whether cocaine patients with prior adversity (as compared to controls and to cocaine patients without prior adversity) would have lower grey matter volume in hippocampal and frontal regions.

Results: *Functional imaging:* Cocaine patients with prior adversity had greater cue-reactivity to 500ms stimuli compared to cocaine patients without prior adversity (cluster-corrected, $p<0.01$, $k>265$). Two patterns of vulnerability emerged: an initial increase in thalamic and midbrain regions, and a sustained response in basal ganglia and caudal orbitofrontal cortical regions. *Structural imaging*. Cocaine participants had lower VBM in several regions compared to controls. However, cocaine patients with prior adversity exhibited greater reductions in gray matter volume as compared to both cocaine patients without adversity, and to healthy controls (cluster corrected, $p<0.005$, $k>88$). This structural difference between patients with and without prior adversity was most striking for regions in and around the temporal lobe (e.g., parahippocampus, hippocampus, fusiform).

Conclusions: In accord with our predictions, these results indicate that cocaine patients with prior adversity (vs. those without) have an increased vulnerability to relapse-relevant cocaine stimuli, as well as more severe reduction of grey matter volume in regions associated with memory, emotion, and stress.

To our knowledge, this endophenotype is the first demonstration that humans with prior adversity may have an enhanced response to appetitive (drug) stimuli – underscoring the interaction between the motivational circuits for reward and aversion. Encouragingly, pilot data suggests that this new adversity-driven, cue-vulnerable endophenotype demonstrates a differential sensitivity to GABA B agonism, highlighting this heterogeneity as useful tool for medication development.