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# Shared Microstructural Features of Behavioral and Substance Addictions Revealed in Areas of Crossing Fibers

Sarah W. Yip, Kristen P. Morie, Jiansong Xu, R. Todd Constable, Robert T. Malison, Kathleen M. Carroll, and Marc N. Potenza

## ABSTRACT

**BACKGROUND:** Similarities between behavioral and substance addictions exist. However, direct neurobiological comparison between addictive disorders is rare. Determination of disorder specificity (or lack thereof) of alterations within white matter microstructures will advance understanding of the pathophysiology of addictions.

**METHODS:** We compared white matter microstructural features between individuals with gambling disorder (GD) ($n = 38$), cocaine use disorder ($n = 38$), and healthy comparison ($n = 38$) participants, as assessed using diffusion-weighted magnetic resonance imaging. To provide a more precise estimate of diffusion within regions of complex architecture (e.g., corticolimbic tracts), analyses were conducted using a crossing-fiber model incorporating local-orientation modeling (tbss_x). Anisotropy estimates for primary and secondary fiber orientations were compared using analyses of variance corrected for multiple comparisons across space using threshold-free cluster enhancement ($p_{\text{familywise error}} < .05$).

**RESULTS:** A main effect of group on anisotropy of secondary fiber orientations within the left internal capsule, corona radiata, forceps major, and posterior thalamic radiation involving reduced anisotropy among GD and cocaine use disorder participants in comparison with healthy comparison participants. No differences in anisotropy measures were found between GD and cocaine use disorder individuals.

**CONCLUSIONS:** This is the first study to compare diffusion indices directly between behavioral and substance addictions and the largest diffusion-weighted magnetic resonance imaging study of GD. Our findings indicate similar white matter microstructural alterations across addictions that cannot be attributed solely to exposure to drugs or alcohol and thus may be a vulnerability mechanism for addictive disorders.

***Keywords:*** Alcohol use disorder, Behavioral addiction, Diffusion tensor imaging (DTI), Impulsivity, Pathological gambling, Substance use disorder

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Neuroimaging data suggest similarities between behavioral and substance addictions that may relate to disease etiology (1–9). However, direct comparisons between addiction subtypes are needed to confirm this hypothesis and to advance pathophysiological understanding of disorder subtypes via identification of unique versus shared neurobiological characteristics (10), as is consistent with ongoing transdiagnostic research efforts (11–13).

Alterations within white-matter (WM) tracts, as assessed using diffusion-weighted magnetic resonance imaging (dMRI), have been reported among individuals with gambling disorder (GD) (1–3) and with substance addictions including cocaine use disorder (CUD) (6,7,14), consistent with theories of common mechanisms of addictions (3). In addition, recent studies indicate neural functional similarities between CUD and GD (4,9). However, the extent to which neural structural alterations are truly shared across addictive disorders has not been assessed previously. Identification of common and distinct neural structural features of addiction subtypes may be used to guide development of novel interventions based on known brain features, particularly as dMRI measures have been shown to link to neurocognition and behavior and may be sensitive to behavioral and pharmacologic interventions (3,15–17). Therefore, this study tests the hypothesis of shared WM tissue alterations between behavioral and substance addictions via comparison of dMRI measures from individuals with GD, individuals with CUD, and healthy comparison (HC) individuals.

All previous dMRI studies of GD (1–3) and CUD (6,7,14,15,18–25) have utilized tensor-derived indices of diffusion such as fractional anisotropy (FA), mean diffusivity, and parallel (axial) and perpendicular (radial) diffusion. Interpretation of these measures is relatively straightforward within the context of anatomical structures with uniform fiber orientations (26), such as the corpus callosum (27). However, within the context of more complex WM architecture [i.e., when a given

 

voxel contains fibers of different orientations, as in most areas of the brain (28)], interpretation of these measures is more ambiguous, making it difficult to make appropriate inferences with respect to underlying biology (26,29–33). This limitation has been recognized for years (28,33,34), and it was recently estimated that up to 90% of WM voxels contain crossing fibers (28).

To address the ambiguity of tensor-derived measures, newer analytic approaches allow for estimation of diffusion for multiple fiber orientations per voxel and provide more precise estimates of diffusion within regions of complex fiber architecture (26,30,31,35), for example, corticolimbic and association tracts implicated in reward processing and addiction vulnerability, such as the corticospinal tracts, corona radiata, and thalamic radiations (36,37). Reduced FA within these and other regions of complex fiber organization have been reported among individuals with GD and CUD, albeit not consistently across studies [e.g., (2,3,14,18,19)]. Estimation of multiple diffusion orientations for regions of complex fiber architecture in addicted populations may therefore be helpful in reconciling existing data.

We compared dMRI measures between individuals with GD, individuals with CUD, and HC individuals using the crossing fiber model proposed by Behrens *et al.* (35). We hypothesized that individuals with GD and individuals with CUD would exhibit reductions in anisotropy measures when compared with HC participants but would not differ from one another on these measures. Specifically, we anticipated that as in earlier studies of GD and CUD separately (1–3,14,19,20,24), individuals with addictions would have reduced anisotropy within WM tracts including the genu, splenium, internal capsules, thalamic radiations, corona radiata, and superior longitudinal fasciculus.

Given effects of chronic alcohol use on WM (38,39), previous dMRI studies have either excluded GD participants with a history of alcohol use disorder (AUD) (3) or else tried to control for possible effects of AUD histories post hoc (1,2). These approaches have significant benefits (e.g., diagnostic specificity) yet given the high co-occurrence rates of AUD among individuals with GD (40,41), may risk limiting generalizability of findings to real-world clinical populations. To allow for comparisons related to AUD, we included equivalent numbers of GD and CUD individuals with and without histories of AUD (approximately 50% per patient group). Based on previous findings of reduced FA within the corpus genu among individuals with AUD (1,38,39,42,43), we anticipated that reductions in anisotropy measures within the genu would be greater among patients with a history of AUDs than in those without.

Elevated rates of impulsivity have been reported among individuals with a range of addictions, and this has been hypothesized as a shared vulnerability marker across addictions and other disorders (44,45). Thus, a third aim of this study was to assess the relationship between impulsivity and WM characteristics across diagnoses. We anticipated replicating previous findings of negative associations between frontal WM and self-reported impulsivity among individuals with GD and CUD within the anterior corpus callosum (e.g., genu) (1,7).

## METHODS AND MATERIALS

### Participants

GD, CUD, and HC individuals who participated in dMRI protocols as part of ongoing functional magnetic resonance imaging research projects in conjunction with the Center for Excellence in Gambling Research, the Psychotherapy Development Center, and the Clinical Neuroscience Research Unit at Yale University's Department of Psychiatry were considered for inclusion in this study. To increase signal-to-noise for dMRI analyses (46), only participants with two complete dMRI acquisitions (acquired during the same scanning session) of good quality (based on visual inspection by two separate researchers) were considered for inclusion in this study. Other inclusion criteria included a DSM-IV diagnosis of pathological gambling (GD participants only) or cocaine use disorder (CUD participants only) as assessed via Structured Clinical Interview

**Table 1. Demographic and Clinical Characteristics of Participants ($N$ = 114)**

| | Gambling Disorder ($n$ = 38), Mean (SD) | Cocaine Use Disorder ($n$ = 38), Mean (SD) | Healthy Comparison ($n$ = 38), Mean (SD) | $F$ | $p$ | $df$ |
|---|---|---|---|---|---|---|
| Age (Years) | 38.26 (11.76) | 42.45 (6.02) | 38.11 (10.90) | 2.36 | .10 | 111 |
| Education (Years) | 13.11 (1.57) | 12.37 (1.10) | 14.34 (1.91) | 15.48 | <.001[a] | 111 |
| | $n$ (%) | $n$ (%) | $n$ (%) | $\chi^2$ | $p$ | $df$ |
| Gender (Male) | 28 (73.7) | 25 (65.8) | 28 (73.7) | 0.77 | .68 | 2 |
| Tobacco Smoker | 20 (52.6) | 30 (78.9) | 6 (15.8) | 30.61 | <.001 | 2 |
| Alcohol Use Disorder[b,c] | 21 (55.3) | 19 (50.0) | – | 0.21 | .65 | 1 |
| Cannabis Use Disorder[c] | 10 (26.3) | 11 (28.9) | – | 0.07 | .80 | 1 |
| Opioid Use Disorder[c] | 3 (7.9) | 2 (7.4) | – | 0.05 | .94 | 1 |
| Major Depression[c] | 7 (18.4) | 9 (23.7) | – | 0.32 | .57 | 1 |
| Anxiety Disorders[c] | 4 (10.5) | 2 (5.3) | – | 0.72 | .40 | 1 |

[a]Post hoc comparisons indicated significantly fewer years of education among both gambling disorder and cocaine use disorder groups, in comparison with healthy comparison participants. Gambling disorder and cocaine use disorder groups did not differ in years of education.

[b]Two gambling disorder and three cocaine use disorder participants met criteria for a current alcohol use disorder; all other alcohol use disorders were remitted.

[c]Healthy comparison participants were excluded for Axis-I disorders except for possible nicotine dependence. Statistics shown for comparison of gambling disorder vs. cocaine use disorder groups.