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Neurobiology of Compulsive Sexual Behavior: Emerging Science

Compulsive sexual behavior (CSB) is characterized by craving, impulsivity,

social/occupational impairment, and psychiatric comorbidity. Prevalence of CSB is estimated around 3–6%, with a male predominance. Although not included in DSM-5, CSB can be diagnosed in ICD-10 as an impulse-control disorder. However, debate exists about CSB's classification (eg, as an impulsive-compulsive disorder, a feature of hypersexual disorder, an addiction, or along a continuum of normative sexual behavior).

Preliminary evidence suggests that dopamine may contribute to CSB. In Parkinson's disease (PD), dopamine replacement therapies (Levo-dopa, dopamine agonists) have been associated with CSB and other impulse-control disorders (Weintraub *et al*, 2010). A small number of case studies using naltrexone support its effectiveness at reducing urges and behaviors associated with CSB (Raymond *et al*, 2010), consistent with the possible opioidergic modification of mesolimbic dopamine function in reducing CSB. Currently, larger, adequately powered, neurochemical investigations and medication trials are needed to further understand CSB.

Incentive motivational processes relate to sexual cue reactivity. CSB vs non-CSB men had greater sex-cue-related activation of the anterior cingulate, ventral striatum, and amygdala (Voon *et al*, 2014). In CSB subjects, functional connectivity of this network associated with cue-related sexual desire, thus resonating with findings in drug addictions (Voon *et al*, 2014). CSB men further show enhanced attentional bias to pornographic cues, implicating early attentional orienting responses as in addictions (Mechelmans *et al*, 2014). In CSB vs non-CSB PD patients, exposure to pornographic cues increased activation in the ventral striatum, cingulate and orbitofrontal cortex, linking also to sexual desire (Politis *et al*, 2013). A small diffusion-tensor-imaging study implicates prefrontal abnormalities in CSB vs non-CSB men (Miner *et al*, 2009).

In contrast, studies in healthy individuals suggest a role for enhanced habituation with excessive use of pornography. In healthy men, increased

time spent watching pornography correlated with lower left putaminal activity to pornographic pictures (Kühn and Gallinat, 2014). Lower late-positive-potential activity to pornographic pictures was observed in subjects with problematic pornography use. These findings, while contrasting, are not incompatible. Habituation to picture cues relative to video cues may be enhanced in healthy individuals with excessive use; whereas, CSB subjects with more severe/pathological use may have enhanced cue reactivity.

Although recent neuroimaging studies have suggested some possible neurobiological mechanisms of CSB, these results should be treated as tentative given methodological limitations (eg, small sample sizes, cross-sectional designs, solely male subjects, and so on). Current gaps in research exist complicating definitive determination whether CSB is best considered as an addiction or not. Additional research is needed to understand how neurobiological features relate to clinically relevant measures like treatment outcomes for CSB. Classifying CSB as a 'behavioral addiction' would have significant implications for policy, prevention and treatment efforts; however, at this time, research is in its infancy. Given some similarities between CSB and drug addictions, interventions effective for addictions may hold promise for CSB, thus providing insight into future research directions to investigate this possibility directly.

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DISCLAIMER

The content of this manuscript does not necessarily reflect the views of the funding agencies and reflect the views of the authors.

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Somatic DNA Variation in Brain as a Source of Risk for CNS Diseases

Somatic mutation during brain development leads to CNS disorders. A missense mutation in *GNAQ* (R183Q) occurs in affected tissues of persons with Sturge–Weber disease, with a frequency in diseased brain and skin ranging from 3 to 36% (Freed *et al*, 2014). In hemimegalencephaly, somatic mutations in *AKT3* were found in 8–35% of cells in the affected tissues (Freed *et al*, 2014). Somatic mutation in *PSEN1* (P436Q) at a frequency of 18% in frontal cortex caused early-onset Alzheimer's disease (Freed *et al*, 2014). One form of somatic mutation that can contribute to CNS disease risk is mediated by long interspersed nuclear element 1 (L1) retrotransposons (Kaer and Speek, 2013). L1s are 6 kb sequences that spread in the human genome by a copy and paste mechanism, and constitute 17% of the human genome (Upton *et al*, 2015). The frequency of *de novo* L1 retrotranspositions in normal brain is controversial (Upton *et al*, 2015). Most retrotransposition-competent L1s are prevented from retrotransposition by epigenetic mechanisms or interactions with inhibitory proteins (Goodier *et al*, 2013).

Whole genome sequencing of genomic DNA from dorsolateral prefrontal cortex (dlPFC) and liver of three persons with schizophrenia revealed increased *de novo* L1s in specific gene ontologies (GOs; see Table 1; Bundo *et al*, 2014). Using L1-based amplification of dlPFC neuronal DNA from 26

TABLE 1 Gene Ontology Terms with Significant Gene Disruption by *de novo* LINE1 Elements

GO term	p-value (Bundo <i>et al</i> , 2014)	p-value (Doyle <i>et al</i> , ^a)
Plasma membrane part	1.5×10^{-5}	7×10^{-4} ^b
Synapse part	4.4×10^{-5}	8×10^{-4}

^aUnpublished observation. ^bAll p-values Bonferroni corrected.

schizophrenia samples and 26 control samples, we confirmed an excess of L1 retrotransposons in genes within these GOs in schizophrenic, but not in control tissues. There was a fourfold increase of *de novo* L1s in 'synapse part' genes (over the random expectation) in our data. Of the 18 genes with putative *de novo* L1s in our 'synapse part' GO list, 9 were also detected by Bundo *et al*, 2014: *DNM2*, *DNM3*, *DLGAP1*, *GRID2*, *GRIN2A*, *HOMER1*, *GPHN*, *SYNE1*, and *SYN3*. These genes are 'of interest' in schizophrenia research because they support data showing associations with GWAS or animal models of schizophrenia.

Methamphetamine and cocaine increased *de novo* L1s in neuronal cells *in vitro* (Okudaira *et al*, 2014). Thus, we conducted an L1 study of medial PFC neuronal DNA from 30 persons with cocaine addiction and controls. Strong evidence ($p \approx 10^{-6}$) for L1-mediated gene disruption was found in phosphate metabolism and kinase pathways, which were not significant among controls (Doyle *et al*, unpublished observation).

The evidence that somatic brain mutation causes brain disease warrants studies of a range of neuropsychiatric disorders (including rodent models) for similar risk-increasing somatic alleles. As somatic mutation does not convey heritable risk, it may be a mechanism to explain some of the environmental risk for neuropsychiatric diseases. There may be disease-specific L1-mediated gene disruption in certain GOs, such as has been found in schizophrenia and cocaine addiction. New drug development might be directed toward gene pathways disrupted by