therapeutic targets for opioid addiction in both males and females.

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Hormone modulation improves cognition in schizophrenia

Sex and stress hormones are reciprocally regulated and have opposing neurobiological effects (Sinclair *et al*, 2014). Molecular changes in brain sex and stress hormone receptors indicate that these systems are out of balance in people with schizophrenia. Furthermore, increased stress can precipitate the onset or trigger the relapse of psychosis, while low levels of estrogen can exacerbate symptoms in females with schizophrenia (Heringa *et al*, 2015). Also, the sex and stress hormone signaling systems are both activated at a time of increased risk for first developing schizophrenia, during human adolescence, when the prefrontal cortex appears primed to respond to cortisol (Sinclair *et al*, 2011) and when sex steroids are flooding the brain. While we often study these major hormonal systems individually, there is greater awareness that they work in concert and should be considered together.

When the source of peripheral sex steroids are removed, male and female rats will alter their glucocorticoid secretion in response to stress in a gender-specific manner. Thus, one way to modulate the body's reaction to stress is to change sex steroid levels. In addition, high levels of cortisol promote neuronal damage, whereas sex steroids, in particular estrogen, act as neuroprotectants. Males and females have equivalent estrogen receptor (ER) alpha levels in one of the most stress responsive areas of the brain: the human prefrontal cortex (Perlman *et al*, 2005). Thus, stimulation of ER in both males and females may potentially buffer some of the damaging effects of stress.

Historically, the field has approached estrogen as a potential therapy for schizophrenia based on the clinical observation that women can sometimes first manifest the symptoms of schizophrenia later in adult life (>50 years). Because of the known drop in circulating estrogen during female menopause, the obvious strategy was to replace estrogen in these women to test if this could lead to clinical improvement. Most studies suggest that adjunctive estrogens can reduce positive, negative and general symptoms of older women with schizophrenia (Heringa *et al.* 2015). However, long-term estrogen treatment can increase the risk of adverse events. The selective ER modulator raloxifene is an alternative estrogen-based treatment, which has been shown to preserve neural activity and cognition in healthy older men and women. Given that men and women with schizophrenia can express abnormal cerebral cortical ERs (Weickert *et al.*, 2008) and raloxifene could overcome the dominant negative effect of these abnormal receptors on wild-type ER in men and women, we administered raloxifene as an adjunctive treatment to antipsychotics in men and women with schizophrenia to determine the extent to which raloxifene would improve cognitive deficits in schizophrenia. We found that adjunctive raloxifene significantly improved memory and attention and increased hippocampal activity during learning in men and women with schizophrenia (Weickert *et al*, 2015; Kindler *et al*, 2015). Since raloxifene acts as an ER agonist in brain, but can act as an ER antagonist in the periphery, it remains an open question as to how raloxifene may impact stress hormone signaling in schizophrenia.

We do know that estrogen actions are complex. Estrogen can exaggerate stress effects and can augment prefrontal dysfunction during stress in females, but can also protect adolescent females from deleterious effects of social stress (Sinclair *et al*, 2014). In males, testosterone inhibits glucocorticoid secretion. Since raloxifene has potential to increase circulating testosterone levels in men with schizophrenia, it is possible that this increase in testosterone could attenuate the response to stress in men with schizophrenia either directly via testosterone's action on androgen receptor or indirectly on ER via conversion of testosterone to estradiol by aromatase.

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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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