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Impact on Cortical Function of Cocaine Abuse Co-Occurring with HIV

According to the USA Center for Disease Control (<http://www.cdc.gov/>) over 36 million humans are currently living with HIV infection, with 44 000 new infections diagnosed annually in

the USA, often reflecting risky sexual behavior. Substance use disorders (SUD) negatively influence every stage of the HIV/AIDS crisis, and SUD are a major obstacle in combating this global pandemic. Other than marijuana, cocaine is the most frequently abused illicit drug in HIV adults (eg, Martin *et al.*, 2016). Cocaine use is associated with increased likelihood of engaging in risky sex, accelerated disease progression, and non-adherence to antiretroviral treatment. An emerging explanation for this association relates to impulsive decision-making. While both cocaine-abusing and HIV-infected individuals often score higher on cognitive impulsivity tasks, those with the comorbidity tend to show the greatest impulsivity (eg, Martin *et al.*, 2016 and references therein). Human imaging studies point to impairments in prefrontal-subcortical networks in these deficits (eg, Meade *et al.*, 2011). To capture a more mechanistic view and to help identify potential therapeutic targets, my laboratory recently set out to evaluate neuropathophysiology within the medial prefrontal cortex (mPFC) in the context of HIV/AIDS comorbidity. We focused on the principal outputs, ie, pyramidal neurons. As we recently reviewed (Wayman *et al.*, 2015), our initial studies demonstrated that acute exposure to a prominent HIV-1 neurotoxic protein, Tat, induced an enduring mPFC astrogliosis and hyper excitability of mPFC pyramidal neurons that was exacerbated by chronic cocaine exposure. These effects were mediated by over-activation of high-voltage-activated L-type calcium channels and were associated with a Tat-induced increase expression of a calcium channel pore-forming protein, Cav1.2- $\alpha 1c$. To better generalize the phenomenon to the chronic nature of brain exposure to HIV-1 proteins, we subsequently evaluated mPFC pathophysiology in HIV-1 transgenic rats following cocaine self-administration. As predicted by Tat-mediated excitotoxicity, the transgenic rats exhibited enhanced mPFC Cav1.2- $\alpha 1c$ expression, and a pyramidal cell hyper excitability and excitotoxicity (Wesley *et al.*, 2016).

This dysregulation was exacerbated following 2 weeks of withdrawal from cocaine self-administration (Wesley *et al.*, 2016).

These electrophysiological studies provide mechanistic support for a mPFC site of convergence for HIV-1 protein-mediated neurotoxicity and cocaine-induced dysregulation at the level of calcium channels within pyramidal neuronal outputs. Evidence for the behavioral consequences of such dysregulation is emerging, eg, in mice performing five-choice serial reaction-time tasks, DREADD-mediated stimulation of mPFC pyramidal neurons suppresses impulsivity (Warthen *et al.*, 2016), and nifedipine (a brain-penetrant Cav1.2/Cav1.3 calcium channel antagonist) reduces impulsivity (Dudley *et al.*, 2013). Thus, L-type calcium channel activity of mPFC pyramidal neurons may be an important regulator of impulsivity, with both ‘too much’ and ‘too little’ being detrimental. When viewed in the context of cognitive impulsivity in the HIV/AIDS cocaine-abuse co-morbid condition, these channels may be pharmacological targets for promoting healthy decision-making, and, in so doing, reduce HIV transmission and disease progression.

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Mirror Neurons in Psychiatric Disorders: from Neuroception to Bio-behavioral System Dysregulation

Impairments in mind-reading abilities (ie, mentalization, empathy) represent core psychopathological features and key therapeutic targets in patients with schizophrenia (SCZ) and autism spectrum disorders (ASD) (Ciaramidaro *et al*, 2015). A functional mirror neuron system (MNS) is considered a prerequisite of these abilities (see Dinstein *et al*, 2010 for alternative views).

The MNS refers to the brain mirror mechanism that allows one to understand the meaning of actions and emotions of others by internally simulating and replicating them (Van Overwalle and Baetens, 2009). Theories on MNS activity were initially inferred from the finding of specific populations of neurons (ie, mirror neurons) that fired during both action execution and observation in macaques. Further studies confirmed the existence of MNS in humans and identified specific brain regions (middle temporal, inferior frontal and inferior parietal gyri, insula, superior temporal sulcus, and sensorimotor cortex) that have a fundamental role in distinguishing environmental and visceral cues, labeling them as safe or life threatening (Van Overwalle and Baetens, 2009). Some

authors refer to this neural activity associated with risk assessment as ‘neuroception’ (Porges, 2007).

Hyperactive states of the MNS may be responsible for over-attribution of intentions to agents and physical events (hyper-intentionality, aberrant salience), misperception of benign social cues as threats (paranoid delusions), and hallucinations in SCZ; hypoactive states may explain a key clinical feature of ASD, ie the tendency to treat people as devoid of intention (Ciaramidaro *et al*, 2015). These differences in neural system activation patterns, consistent with the RDoC initiative, have led some authors to hypothesize that ASD and SCZ represent extremes on a continuum of mind-reading abilities ranging from a mechanistic hypo-intentional (to treat people as objects) to a mentalistic hyper-intentional (to treat objects as people) mode, respectively (Ciaramidaro *et al*, 2015). Minichino *et al*, (2016) report that both ASD and SCZ patients show impaired event-related desynchronization of mu waves (a proxy of MNS activity) in response to observation of biological motion, which is associated with negative symptoms and poor social adjustment. Synergistic studies, using measures of resting state connectivity, demonstrated that differences in the direction of the modulatory control (excitatory vs inhibitory) of the medial prefrontal cortex and the temporoparietal junctions over the MNS might result in modification of its activity (hyperactive vs hypoactive states), explaining different features of SCZ and ASD.

Connectivity of the MNS with the amygdala, the periaqueductal grey, and the autonomic nervous system (ANS) suggests a top-down control of bio-behavioral systems, including the hypothalamic-pituitary-adrenal axis (HPA), metabolic, and immune systems (Friedrich *et al*, 2014). Altered MNS functional states may indeed lead to the chronic activation and dysregulation of bio-behavioral systems and their bio-mediators (cortisol, sympathetic and parasympathetic transmitters, cytokines, and metabolic hormones), which dynamically interact among each other

and in turn may affect brain plasticity (Friedrich *et al*, 2014).

Although it is well-known that impaired social cognitive skills are strongly associated with poor social outcomes and high levels of distress (Ciaramidaro *et al*, 2015), what is new is the hypothesis that altered neuroception, related to dysfunctional MNS activity, may mediate this relationship (Friedrich *et al*, 2014). Multi-dimensional interventions for ASD and SCZ should ideally target both cortical and peripheral components of this vicious cycle, with interventions aimed at synchronizing MNS and ANS activity such as neurofeedback (Friedrich *et al*, 2014), mindfulness, or yoga practices.

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