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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 (Friederich *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). Multidimensional 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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