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Reply to “The insular cortex and QTc interval in HIV+ and HIV– individuals: Is there an effect of sympathetic nervous system activity?”

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The correspondence by Nagai et al. (2018) first contends that our finding of greater connectivity between left anterior insula (I_a) and ventromedial prefrontal cortex (VMPFC) with shorter QTc interval (McIntosh et al., 2017) is counter-intuitive given the dog model of sympathetic inhibition on QT prolongation. Before we provide an alternate interpretation of our findings we should first emphasize QTc and functional brain connectivity data were collected independent of each other, thus precluding any direct inference of causality.

Indeed, the left I_a is implicated in parasympathetic regulation, however, this structure also plays a unique role in cardiac interoceptive awareness (Oppenheimer and Cechetto, 2016). Considering that the reported measure of resting state functional connectivity (rsFC) reflects trait-like patterns of dependence amongst neural assemblies we offer a cautious interpretation of the increased left I_a connectivity with VMPFC as a pattern of counter-regulatory neural response to the high cardiac contractility indicative of short QTc interval. As Nagai and colleagues alluded afferent and efferent signaling throughout the Central

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Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

Autonomic Network (CAN) allows for cardiocentric interoceptive information to facilitate regulation of cardiac sympathetic and parasympathetic outflow (Benarroch, 1993). As evidenced by animal tracing and human imaging studies, visceral information, including beat-to-beat dynamics, are carried by nerve signals through the medulla, pons, and subcortical brain before terminating in the primary visceral sensorimotor cortex; i.e., anterior insula (Cechetto and Chen, 1990; Craig, 2002). Compensatory feed-forward signaling from the anterior insula and other visceral processing regions to cardiac effectors in the medulla can alter sympathetic innervation of stellate ganglion via the rostral ventrolateral medulla or parasympathetic innervation via the nucleus ambiguus and dorsal motor nucleus of the vagus (Loewy and Spyer, 1990). Nevertheless, for the sake of parasympathetic regulation, efferent control of these cardiac signals are more likely to be propagated via the medial prefrontal cortex and its dense GABA-ergic connections with rostroventrolateral medulla and glutamatergic connections with the inhibitory neurons of the caudal ventrolateral medulla via the NTS (Andresen and Kunze, 1994; Cechetto and Saper, 1990; Chalmers et al., 1992; Chalmers et al., 1994; Guyenet et al., 1987; Verberne, 1996).

This interpretation of greater left I_a and VMPFC connectivity with the short QTc interval phenotype is consistent with other neuroimaging studies citing compensatory parasympathetic responses to sympathetic perturbation. For instance, Gray and colleagues observed that increased blood pressure response without commensurate changes in heart rate, following a series of synchronously applied shocks (indicative of ventricular contractility, dromotropy and inotropy from left stellate ganglion stimulation), subsequently increased activity of the left I_a and brainstem medulla (Gray et al., 2009). Others have shown greater parasympathetic tone (indexed by heart rate variability) in response to emotional perturbation was associated with increased activity in the MPFC and left I_a again suggesting a paradoxical effect for sympathetic cardiovascular stimulation on co-activation of the vagal and interoceptive structures such as the VMPFC and I_a (Lane et al., 2001). Thus, within the inherent limitations of our study design, we propose the increased connectivity between left VMPFC and I_a may reflect interoceptive signaling of a compensatory neural response to a marker of increased ventricular contractility, i.e., shortened QTc interval at rest (Huang et al., 1995).

With regards to our finding of greater rsFC between VMPFC and right posterior insula (I_p) in persons with longer QTc interval length, Nagai and colleagues also astutely pointed out that right I_a appears to play a greater role in the orchestration of sympathetic responses than does the right I_p . Single-unit recordings in rodents and monkeys suggest that right I_p contains a higher concentration of baroreceptive, i.e., blood pressure change responsive cells than left I_p (Oppenheimer and Cechetto, 1990; Zhang et al., 1998). In the rat, reciprocal projections from the parabrachial nucleus and NTS facilitate both pressor and depressor responses upon microstimulation of the I_p (Saper and Loewy, 1980; Saper, 1982). Moreover, microstimulation of the rostral portion of the I_p results in the pressor response while a greater proportion of depressor sites have been identified in caudal regions of the rat I_p (Yasui et al., 1991). Combined with the observation that in humans right I_p shows greater rsFC with the left I_a at rest than any other cortical area supports the role of right I_p in orchestrating depressor baroreflex responses (Cauda et al., 2011). In our study, the long QTc interval phenotype exhibited by HIV+ and HIV- negative men was associated with greater

rsFC between the VMPFC and several clusters within in the caudal portion of the right I_p. Thus, increased connectivity between the VMPFC and right I_p might reflect a depressor/parasympathetic phenotype of neural activity that is indicative of long QTc interval length (Wong et al., 2007; Ziegler et al., 2009).

In sum, our findings are in support of lesion and neural stimulation studies implicating a key role for the insula cortex, amongst other CAN structures, in top-down regulation of cardioautonomic function (Nagai et al., 2017; Oppenheimer and Cechetto, 2016). Within the context of VMPFC connectivity the patterns observed in the left and right insula may speak to the neurovisceral integration feature of insular cortex (Thayer and Lane, 2009). In our study, the key distinction between the resting QTc phenotypes and VMPFC connectivity with the left anterior versus right posterior insula appears to be the role of these circuits in detecting sympathetic stimulation versus facilitating compensatory parasympathetic responses, respectively. Nevertheless, it should be emphasized that the connectivity patterns in relation to QTc interval length did not survive voxel-wise correction and thus should be interpreted with caution (Woo et al., 2014). In order to further elucidate potential neurogenic sources of cardiac manifestations in chronic HIV disease patients future studies may need to compare QTc interval length with moment-to-moment changes in whole brain functional connectivity of the insula cortex. Doing so may further understanding of the role of this structure in cardioautonomic regulation.

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