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Aberrant left insular cortex response: A possible pathogenesis of reduced vagal nervous system activity in heart failure? - Reply

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We thank Dr. Nagai and co-authors for their interest and comments in our work. We described recently (Song, Roy, Fonarow, Woo, & Kumar, 2018) decreased neural activation in the left insula during the Valsalva maneuver in heart failure (HF). However, the functional differentiations between anterior and posterior insular cortices were not explored extensively due to the primary focus for examining correlations between brain structural changes and impaired functional responses during the Valsalva challenge in the condition.

Multiple studies supported the notion that the right insular cortex is associated with sympathetic activity, and left insular cortex with parasympathetic control (de Morree, Rutten, Szabó, Sitskoorn, & Kop, 2016; Hilz et al., 2001; Nagai, Hoshida, & Kario, 2010). In addition, our group also showed a right-sided dominant insular responses to a static handgrip challenge for both left- and right-handed tasks (Macey et al., 2012). Thus, the decreased left insular responses to the Valsalva maneuver reported here might be associated with reduced vagal nervous system activity in HF.

Although we missed the opportunity to examine variable response patterns between anterior and posterior insular regions to the Valsalva maneuver in HF, our previous study from healthy subjects shed lights on such variations (Macey et al., 2012). We found differed responses in both the right and left insular cortices during strain phase of the Valsalva maneuver between gyri in an anterior-posterior order, with greater responses in the anterior gyri (Macey et al., 2012). In addition, the anterior, mid, and posterior short right insular gyri responded similarly, but the left insular activity was greatest in the anterior gyri, followed by

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the mid short gyri, which was greater over the posterior short gyri (Macey et al., 2012). Given the preferential left-sided parasympathetic dominance, findings suggest that sympathetic regulation on the left insula is greatest in the most-anterior gyri, but sympathetic regulation is similar across all three right anterior insular gyri (Macey et al., 2012). Consistently, our current study showed significant activations in bilateral anterior insula in healthy controls during the Valsalva challenge, suggesting that the anterior insula has stronger association with sympathetic control than the posterior part.

In the Valsalva maneuver, the challenge phase is characterized by a large and rapid increase in sympathetic activity, reflected as increased heart rate, and the recovery phase includes parasympathetic activation. However, we have described prolonged and aberrant sympathetic activity during the Valsalva maneuver in HF subjects (Woo et al., 2007). In this study, we found decreased left insula responses in HF patients in the anterior and middle portions, but not in the posterior area. This discrepancy may have resulted due to the computational model used to compare the challenge phase over baseline period. Also, poor temporal resolution and inter subject variability between end stage of sympathetic and initiation time of para-sympathetic may have contributed to mask-out anterior- posterior insular differences on the left side. Although the present findings support a right-sided and anterior insular dominance for sympathetic activities, further studies adopting procedures that probe pure vagal nervous system activities with better temporal resolution are required to confirm the role of posterior left insula in autonomic regulations.

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