Journal Club

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Disentangling the Association between the Insula and the Autonomic Nervous System

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Review of Kucyi and Parvizi

In everyday life, we are continuously exposed to numerous stimuli that we either neglect or consider according to our own goals and preferences. The ability to filter competing stimuli and attribute importance to relevant information, known as salience detection, is supported by the dorsal anterior insula (daI; Uddin et al., 2017). Mounting evidence suggests that there is a bidirectional relationship between the daI and the autonomic nervous system, such that the insula is sensitive to interoceptive information (e.g., heart rate or blood pressure), but also modulates the autonomic system to maintain sensory homoeostasis or increase perception (Craig, 2009; Cechetto, 2014; Uddin et al., 2017). The mechanisms by which the daI modulates the autonomic system are not fully understood, but a recent study by Kucyi and Parvizi (2020) exploring pupil dilation provides new insights into the links among the insula, the autonomic system, and perception.

Pupil dilation is an autonomic response to increase visual sensitivity (Mathôt, 2018). Previous reports have demonstrated an association between phasic pupil dilation and increased activity in the insular cortex during error monitoring (Harsay et al., 2018) and emotional perception (Paulus et al., 2015; Tamietto et al., 2015; Leuchs et al., 2017), suggesting that the observed coupling between the pupil and the daI may occur in relation to the detection of salient stimuli. However, at the present time the temporal properties of this coupling, particularly across distinct arousal states or tasks, remains unclear.

In their recent study, Kucyi and Parvizi (2020) used human intracranial electroencephalography (iEEG) and pupillometry to measure task-evoked and spontaneous daI activity and pupil dilation in three subjects undergoing neurosurgical treatment for refractory focal epilepsy. This approach enabled them to explore temporal patterns, spectral properties, and spatial localization of insular cortex activity, as well as to determine whether differences in amplitude or time delay occur in the daI–pupil coupling. Subjects performed a minimum of 15 min of wakeful rest with visual fixation, as well as four to eight 6 min runs of the gradual-onset continuous performance task (Esterman et al., 2013), during which electrophysiological data and pupil diameter were simultaneously recorded. In the task, participants were shown grayscale images of cities (90% of the images) and mountains (10%). They were instructed to press a key if the currently displayed city image differed from the previous one, and to withhold from responding if a mountain image appeared. Importantly, transitions from one image to the next occurred gradually via linear pixel-by-pixel interpolation of the scenes over an interval of 800 ms. As a result, images were best discernible 400 ms after trial onset (image coherence peak), and then started to fade out in the transition to the next scene. Participants' responses were classified as correct commissions (response to city), omission errors (no response to city), correct omissions (no response to mountain), or commission errors (response to mountain) by means of a specific criterium based on the comparison between the reaction time and the level of coherence of the presented image.

Task-evoked iEEG responses were analyzed based on the high-frequency broadband (HFB) signal (70–150 Hz), a key analytical signal in human intracranial recordings measuring brain activity (Leszczyński et al., 2020). For each participant, electrodes showing significantly higher HFB signal in response to target stimuli (i.e., mountains) than to nontarget stimuli (cities) were largely clustered in the daI. This increase of daI activity occurred in both correct and incorrect behavioral responses to target stimuli (withheld and button press, respectively), which is in line with previous reports of daI activation in relation to both salience detection and error monitoring. The magnitude and timing of the HFB signal in the identified

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electrodes was then compared with the normalized pupil response. The following four noteworthy results emerged: (1) spontaneous activation of the daI exhibited the same spatial, spectral, and temporal profile as task-evoked activation; (2) changes in pupil size were time locked with both spontaneous activity and evoked responses in daI; (3) task-evoked responses in daI preceded and correlated with the magnitude of evoked pupil dilations; and (4) highly salient stimuli induced greater activation of the daI and greater pupil dilation than low-salience stimuli or rest. Together, these findings suggest that the observed daI–pupil coupling concerns both the time and the amplitude of daI activity, while also being independent of the experimental condition (task or rest).

The strong coupling between daI activity and pupil size described by Kucyi and Parvizi (2020) has provided new information to supplement the pupil dilatation pathway. The iris dilator muscle responsible for pupil dilation is controlled by the sympathetic nervous system, the branch of the autonomic nervous system that regulates arousal and wakefulness. The sympathetic nervous system is in turn modulated by the locus coeruleus, the primary noradrenergic nucleus modulating pupil diameter (DiNuzzo et al., 2019; Peinkhofer et al., 2019). Interestingly, the locus coeruleus shows reciprocal innervations with the insula (Aston-Jones and Cohen, 2005). By documenting robust coupling between pupil diameter and daI activity across different conditions, Kucyi and Parvizi (2020) provided evidence for the involvement of the daI in the pupil dilation pathway, where both the timing and amplitude of daI activity predict pupil dilation. This has a remarkable impact in the field, showing the important role of the insula within the neural pathway of pupil dilation. Given that both the insula and the locus coeruleus affect pupil size, it appears that the exact neural pathway of pupil dilation may in fact be more complex than previously thought and has still to be fully revealed. Therefore, understanding how the interactions between the insula and the locus coeruleus impact pupil dilation requires further investigations. High-temporal resolution measures, such as those used by Kucyi and Parvizi (2020), as well as connectivity measures would be beneficial to achieve this goal.

Furthermore, the daI–pupil coupling shown by Kucyi and Parvizi (2020) highlights the interactions between daI and the autonomic system leading to an increase in visual sensitivity, which fits with the known roles of the daI and the autonomic system in salience and arousal, respectively. As a result, such daI coupling increases the amount of visual information when a behaviorally relevant stimulus is detected, which may in turn facilitate decision formation (Strauch et al., 2018), error monitoring (Maier et al., 2019), and adaptive behavior (Maier et al., 2019).

On a separate note, the present study also raises important questions regarding the potential consequences of insular damage on pupil activity, and more broadly on behaviors that involve an efficient daI coupling. We note the potential utility of adopting this approach in neurodegenerative disorders such as frontotemporal dementia (FTD), in which structural and functional abnormalities of the insular cortex are prominent early features (Kumfor et al., 2015; Whitwell, 2019). Mounting evidence suggests that degeneration of the insular cortex relates to autonomic dysfunction in FTD (Ahmed et al., 2018). Additionally, a recent study indicates that pupil dilation in response to salient sounds is reduced in people with FTD (Fletcher et al., 2015). The findings by Kucyi and Parvizi (2020) suggest that decreased pupil dilation in FTD may stem from degeneration in the dorsal anterior insula, although this intriguing proposal requires formal testing. In addition to insular atrophy, FTD manifests with noradrenergic abnormalities resulting from protein deposits in the locus coeruleus. Thus, multiple sites of degeneration might explain decreased pupil dilation in FTD. Accordingly, reduced pupillary dynamics in FTD may result from atrophy in the brain areas supporting cognitive control of the autonomic system, as well as in the autonomic system itself.

Based on the findings of Kucyi and Parvizi (2020), compromised daI–pupil coupling in dementia may lead to reduced detection of relevant stimuli and visual sensitivity across a variety of cognitive tasks and conditions. For example, reduced salience detection may impact performance in any task requiring the detection of unexpected events. It may also prevent task switching as required by a suddenly changing environment. Dysfunctional autonomic responses to relevant stimuli may not only reduce perceptual sensitivity, but also negatively affect arousal. Consequently, cognitive and behavioral abnormalities resulting from impaired salience detection are to be expected in dementia, and across multiple domains. A comprehensive understanding of the interactions between salience detection and the autonomic system in dementia will therefore provide crucial insights into the early detection and management of these debilitating conditions.

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