Imaging the Brainstem: Approaches, challenges and opportunities

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Symposium

The past few years have witnessed renewed interest in the brainstem within the neuroscientific, neuropsychological and clinical fields. The brainstem hosts multiple structures that constitute key centers for arousal and consciousness, pain, autonomic function, and cortical neuromodulation. Brainstem structures present challenges when assessing their location and activity through neuroimaging methods in humans, making the use of standard preprocessing and analysis toolboxes and pipelines insufficient or inadequate. In spite of this, recent efforts have advanced the field and took it to a point where theoretical or conceptual postulates about the role of brainstem systems can be tested. Improvements in brainstem mapping have the potential to lead to a better understanding of its functional interaction with cortical systems, its relation to physiological signatures, its involvement in higher-order functions, and its prominent role in multiple psychiatric and neurological conditions. This symposium intends to give an overview of technical and neuroscientific state-of-the-art of brainstem imaging work by experts who have intensely researched brainstem systems in humans, with a particular focus on neuromodulatory systems. The program includes topics such as: technical approaches to the imaging of small structures, opportunities offered by high-field MRI, promises of brainstem-specific measures as biomarkers in brain disorders, assessment of brainstem nuclei activity during cognitive processes, and use of ocular measures to inform brainstem structures mapping. The symposium puts the brainstem in the spotlight and is intended for everyone who is interested in unveiling the brainstem's fascinating mysteries.

Objective

The symposium aims to equip the audience with answers to the following questions, presenting them in the context of current research lines.
-What has recent brainstem imaging research revealed about brain function and cognition? What is the relevance of brainstem imaging for the study of brain pathologies?
-What technical challenges do we face when imaging the brainstem? How could one take advantage of high-field fMRI?
-How can physiological measures inform brainstem activity measures?

Target Audience

The symposium is aimed at a broad audience interested in complementing human cortical mapping with the mapping of subcortical structures located in the brainstem, and exploring the role of brainstem structures in cognitive function and dysfunction. The symposium is also suitable for more specialized researchers interested in technical aspects of brainstem imaging as well as the combination of physiological measures with brainstem activity.

Presentations

Brainstem Modulation of Cortical Network Activity and Cognitive Behavior

The ascending arousal systems of the brainstem send widespread projections to the cerebral cortex, from which they release modulatory neurotransmitters. This puts the brainstem systems in the position to control the state across large parts of cortex and, thereby, shape cognitive computation. Critical experimental data pertaining to this interplay between brainstem activity, cortical network activity, and cognitive computation are so far limited. In a series of studies, we combined fMRI of brainstem and cortical network activity in humans with recordings of pupil diameter (a peripheral measure of arousal state) and modeling of cognitive behavior. We focused on the following major neuromodulatory nuclei: the cholinergic basal forebrain, the dopaminergic ventral tegmental area and substantia nigra, the serotonergic dorsal raphe nucleus, and the noradrenergic locus coeruleus. We quantified intrinsic correlations of activity among these nuclei, as well as with cortical activity and non-luminance-mediated changes in pupil diameter, during rest and elementary perceptual choice tasks. For the latter, we exploited trial-to-trial fluctuations of task-evoked responses. We used anatomical atlases or individual structural scans to delineate brainstem nuclei and monitored respiratory and cardiac activity to remove resulting artefacts from the fMRI data. Our approach uncovered robust activity correlations among the different brainstem nuclei, as well as robust and unique contributions of several nuclei, in particular the locus coerulues, with fluctuations of pupil and widespread cortical activity. During task, these brainstem responses predicted a reduction of the impact of pre-existing biases (or priors) on the perceptual decision. In sum, brainstem arousal systems account for a substantial part of ongoing variability in cortical activity and behavior, through widespread cortical state changes on different timescales. Thus, the brainstem is an important player in the orchestration of intrinsic co-fluctuations in cortical neuroimaging signals, which are commonly interpreted as direct expressions of intra-cortical network interactions.

Presenter

Tobias Donner, University Medical Center Hamburg-Eppendorf Hamburg, Germany

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Catecholaminergic Systems Help Construct Memories of Time and Discrete Events

Pisodic memories do not strictly mirror the constant stream of experience. Rather, they come to reflect the passage of discrete and meaningful events. Recent work shows that pupil-linked arousal measures help signal this transformation of continuous experience into memorable episodes (Clewett et al., 2020). However, the specific arousal-related mechanisms that facilitate this process of memory segmentation are unclear. Here, we used a combination of high-resolution functional magnetic resonance imaging (fMRI), neuromelanin MRI, and pupillometry to examine if arousal-related catecholaminergic systems influence the temporal organization of events in memory. While in the MRI scanner, participants encoded lists of object images as they listened to simple auditory tones in their left or right ear. At infrequent yet regular intervals within each sequence, the tone switched to the participant's other ear to create an 'event boundary' that divided each item sequence into discrete auditory sub-events. Replicating prior work, we found that these auditory event boundaries elicited increased pupil dilation, impaired temporal order memory, and led to more exaggerated retrospective estimates of temporal distance between items from recent event sequences. Interestingly, these objective and subjective temporal memory effects were associated with different patterns of neuromodulation at event boundaries: whereas impaired temporal order memory was related to increased LC activation, subjective time dilation was related to increased ventral tegmental area/substantia nigra (VTA/SN) activation. Both temporal memory effects were also associated with periods of higher pupil variability across encoding, consistent with the idea that arousal provides a strong internal context for both linking and separating event representations in memory. Taken together, our findings suggest that along with fluctuations in arousal, the noradrenergic and dopaminergic systems may differentially influence memory representations of temporally-adjacent events.

Presenter

David Clewett, University of Southern California Los Angeles, CA, United States

Elucidating the Contribution of In Vivo Measures of Locus Coeruleus Structure and Function to Alzheimer's Disease-Related Pathology and Cognitive Decline

Background: The key pathological hallmarks of Alzheimer's disease are amyloid-beta (Aβ) and tau accumulation. These proteinopathies start to accumulate decades prior to the first clinical symptoms. In fact, autopsy studies reported that the locus coeruleus, a small pontine nucleus providing norepinephrine to the brain, is the first site accumulating tau pathology early in life. In vivo assessing the locus coeruleus is complicated due to its size, its proximity to the fourth ventricle and the influence of physiological noise. We developed methods to examine the function and structure of the locus coeruleus in vivo and aimed to examine their association to Alzheimer's disease pathology and cognitive function. Methods: We examined three different samples: 1) Participants (n=172) from the longitudinal Harvard Aging Brain Study (HABS) who underwent MRI imaging, Aβ and tau-PET imaging and longitudinal cognitive assessments 2) Participants from HABS (n=128) who participated in functional MR imaging involving a novelty task, underwent Aβ PET imaging and longitudinal cognitive assessments and 3) Participants from a 7T MRI lifespan study (n=99) who also underwent cognitive assessments and biomarker assessments. In all samples we examined the relationship between locus coeruleus MRI measures, pathology and cognition using linear regression or mixed-effects models (with age, sex and education as covariates). Results: For our structural measures, we found that lower locus coeruleus integrity was associated with greater deposition of tau in the entorhinal cortex, these associations extended beyond the medial temporal lobe when Aβ was elevated. Furthermore, lower locus coeruleus integrity was associated with retrospective Aβ-related memory decline. In our functional analyses, we observed greater locus coeruleus activity and connectivity with the medial temporal lobe during novelty as compared to repetition of stimuli. Activity and connectivity of the locus coeruleus was not modulated by Aβ deposition. But, individuals with lower novelty-related locus activity or connectivity exhibited greater decline on the preclinical Alzheimer's disease related composite when Aβ was elevated. Discussion: These findings identify structural and functional alterations in the locus coeruleus as a promising indicator of initial Alzheimer's disease-related processes and may predict subtle changes in future cognitive trajectories of preclinical Alzheimer's disease.

Presenter

Heidi Jacobs, Massachusetts General Hospital/Harvard Medical School Boston, MA United States

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Imaging Brainstem Structures: Methodological aspects

The brainstem is packed with structures that participate in a large variety of brain functions, including autonomic regulation, sensory-motor relays, consciousness and arousal, pain, and neuromodulation of higher-order functions. Therefore, the ability to single out the activity and connectivity properties of these structures has great scientific and clinical relevance. Brainstem structures have been studied for many years in humans using histological and neuroimaging methods (including positron-emission tomography and magnetic resonance imaging). Efforts towards a standardization of neuroimaging techniques for subcortical structures, including the brainstem, have identified several factors to be addressed when intending to complement whole-brain imaging with brainstem measures. This talk will offer an overview on the current state of our ability to image activity in the brainstem, highlight some of those methodological aspects, and exemplify these with our work on converging approaches for measuring activity in small structures, the investigation of the BOLD response in brainstem nuclei, and the use of physiological measures to assist analysis of brainstem activation and interpretation.

Presenter

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