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Research report

Regional and long-range neural synchronization abnormality during passive hyperthermia

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ABSTRACT

Passive hyperthermia would impair wide-domain cognitive performances (e.g. attention, working memory), which may involve abnormal regional and long-range neural activity. Combining the regional homogeneity (ReHo) and seed-based functional connectivity analysis, this study investigated the regional and long-range neural synchronization abnormality during passive hyperthermia. We acquired the resting-state blood oxygenation level dependent (BOLD) data from twenty-three healthy male participants in two simulated thermal conditions: normothermic condition (NC) with temperature at 25°C for 1 h and hyperthermic condition (HC) with temperature at 50°C for 1 h. After scanning, participants were asked to perform an attention network test (ANT). Relative to NC participants, the participants in HC group exhibited decreased regional neural synchronization in the frontal-occipital cortex, specifically in the left opercular part of inferior frontal gyrus/insula, bilateral middle occipital gyrus, and posterior cingulate cortex/precuneus, but increased one in the left dorsal superior/middle frontal gyrus. Using these significantly differed ReHo clusters as seeds, we further performed functional connectivity analysis and found aberrant long-range neural synchronization in the orbital medial frontal cortex, temporal-parietal junction areas. Further neurobehavioral correlation analysis showed significant positive correlation between the regional ReHo alteration in left dorsolateral superior/middle frontal gyrus and executive control effect. Additionally, the functional connectivity of the orbital medial frontal cortex with the seeds "left superior/middle frontal gyrus" and "posterior cingulate cortex/precuneus" were negatively correlated with the increase of rectal temperature. In current study, the participants showed hyperthermia-induced brain activity disruptions, appearing as altered local ReHo and long-range functional connectivity, which might help understand the relationship between neuronal and circuit activities and physiological thermal sensation and regulation as well as behavioral changes.

1. Introduction

Environmental hyperthermia poses much risk to many occupational workers [1]. Thermal sensation and regulation system balances internal heat production and heat dissipation through thermal receptors in the superficial skin, spinal cord and central nervous system [2–4]. Once thought of as a simple physiological process, converging altered wide-domain cognitive performances during hyperthermia have been demonstrated, such as attention, short term memory and tracking performance that often resulted in workplace accidents [5–7]. It is important to illuminate the neurological correlates of cognitive dysfunction during hyperthermia to help develop neurophysiological prevention strategies in such environment.

Brain EEG and functional imaging studies have demonstrated altered brain activity and cortical activation patterns in resting-state, visual attention network task, working memory task during whole body hyperthermia [3,7–10]. Hyperthermia also affects certain aspects of cognitive performance. In an attention network task, Sun, et al. [7] found that the passive hyperthermia impaired executive control but not orienting and alerting performance. Using another task paradigm, Gaoua, et al. [11] observed impairment in working memory but not attentional process during hyperthermia. Recently, functional magnetic resonance imaging provides excellent opportunities to investigate cognitive dysfunction during hyperthermia [8–10,12–15]. Using attention network test, Liu, et al. [9] reported enhanced activation in dorsolateral prefrontal cortex (DLPFC), temporal lobe, middle occipital gyrus and inferior parietal lobule, correlated with aberrant executive control performance. It appears that the frontal lobe and parietal lobe

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are susceptible to hyperthermia. Jiang, et al. [10] also found enhanced activation in bilateral DLPFC and right intra-parietal sulcus during hyperthermia in visual short-term memory task performing. Regarding long-range brain connectivity, Qian, et al. [12] investigated inter-regional functional connectivity in whole brain, and found that decreased brain connectivity was mainly involved with the medial orbital frontal cortex, temporal lobe and occipital lobe, increased one was mainly located within limbic system.

However, these previous studies mainly focused on either regional activation or network-level functional connectivity [8–10,12]. The potential relationship between regional and long-range brain connectivity was neglected. It has been previously proposed that across normal brain development, the organization of multiple functional network shifts from "local to distributed" characterization, which has important implications for neural substrate of cognition [16]. Moreover, previous studies have reported that the alterations of regional neural synchronization could further result in alterations of functional connectivity in several brain disorders, including schizophrenia, subjective tinnitus, and relapsing-remitting multiple sclerosis [17–19]. Compared to analysis with a single index, the conjoint analysis of regional and long-range connectivity could provide more information about altered brain activity. As effective indicators reflecting both the regional and long-range intrinsic organization of human brain, regional homogeneity (ReHo) and functional connectivity have been conjunctively used in exploration of brain diseases and aging[20–22]. These two indices have been proved to be mutually complementary for investigating regional and long-range neural synchronization. ReHo calculates the similarity of the time series of one voxel to its nearest neighborly voxels in a voxel-wise manner, reflecting intraregional neural connectivity [23]. Functional connectivity, which calculates temporal coherence of brain regions in long distance [24], might provide more information about interregional neural connectivity alterations in the complex and collaborative brain system.

To this end, we employed resting-state functional magnetic resonance imaging (fMRI) approach to elucidate both regional and long-range brain connectivity during hyperthermia. Methodologically, similar to the research strategy used by Liu, et al. [25], analyses was processed in three steps. Firstly we examined whether specific ReHo patterns were differentially disrupted during whole body hyperthermia. Secondly, we determined whether the clusters with significant regional disruptions had altered functional connectivity with other brain regions. Thirdly, we explored whether regional and long-range brain connectivity was related to behavioral and physiological measures.

2. Materials and method

2.1. Participants and experimental design

The present study incorporates data from our previous resting-state fMRI study [12]. Briefly, eighteen healthy male college students were recruited in this study. Female participants were excluded in the present study, as menstrual cycle would cause possible fluctuations in hormone levels, basal body temperature, and behavior reaction time [26,27]. All of them had no history of neurological, psychiatric disorders, brain traumatic injury or substances abuse. The study protocol was approved by the Jinan Military General Hospital Ethical Committee. To increase the sample size, we recruited another ten students with similar demographic characteristics into current study to reach a total of 23 participants (after removing 5 participants, see our explanation below) in our combined analysis. It needs to be stated that the previous study mainly focused on the topological patterns of large-scale brain functional networks using graph theoretical analysis. The present study intends to investigate the regional and long-range neural synchronizations using ReHo and functional connectivity analysis, which are not replicate of previous study.

Every participant underwent two thermal conditions in an environmental chamber. One is normothermic condition (NC) with temperature 25°C and relative humidity 60% for 40 min. Another is hyperthermic condition (HC) with temperature 50°C and relative humidity 60% for the same time period. Each participant underwent both thermal exposure conditions in a counter-balanced order with 3–7 days apart. Before entering the chamber, each participant wore a thermal lab-suit covering the whole body, as well as head. The suit was embedded with a soft pipe in which the hot water would flow. After 40-min thermal exposure in the chamber, the participants were taken to the MRI room for scanning. Before scanning, the pipe in the suit was connected to subsidiary water temperature control device. During scanning, the temperature in the suit was the same as the chamber for each condition. The MRI scanning took about 20 min. Rectal temperature and dehydration before entering the chamber and after fMRI scanning were measured. After this, the participants were taken back to the environment chamber, and performed a modified attention network task which was used by Fan, et al. [28]. Three attentional networks, including executive control, alerting and orienting networks were tested using three cue conditions (no cue, center cue and spatial cue) and two target types (congruent and incongruent). The detailed information about this task can be seen in our previous studies [7,12]. Reaction time (RT) for different cues and target conditions reflected the efficiency of three attentional networks, and was calculated by following formulas:

$$\textit{Alerting effect} = RT_{no\ cue} - RT_{center\ cue};$$

$$\textit{Orienting effect} = RT_{center\ cue} - RT_{spatial\ cue};$$

$$\textit{Executive control effect} = RT_{incongruent} - RT_{congruent};$$

The heat exposure protocol used in the present study was similar with the one in previous studies [6,11,29–33]. Considering that the participants would undergo heat exposure for some time during MRI scanning which required them to keep motionless, we made corresponding strategies to ensure the safety of the experiment. Firstly, we lower the heating intensity. The temperature was similar with the one in previous studies [6,11,29–33], whereas the heat exposure duration was much shorter. Specifically, the total duration of heat exposure in the present study was about 1 h, while it took about 2 h, even much longer in other previous studies. Secondly, participants were asked to wear self-developed special suits with a protective layer between the skin and heating suit in order to avoid direct touch to the heat suit. Thirdly, during the scanning, all the participants had rights to discontinue the experiment if they felt very uncomfortable.

2.2. Data acquisition and analysis

The resting-state scans were obtained for all of the participants using a GE Signa 1.5 T scanner (General Electric, Milwaukee, Wisconsin). The participants lay in a supine position with their heads fixed in place by foam pads to minimize head translation and rotation movements. Each scan consisted of 200 EPI functional volumes with the following parameters: TR = 2000 ms, TE = 40 ms, flip angle (FA) = 90°, number of slices = 29, matrix = 64 × 64, field of view (FOV) = 24 × 24 cm^2, thickness/gap = 4/0 mm, acquisition voxel size = 3.75 × 3.75 × 4 mm^3. Additionally, a high resolution T1-weighted sequence was obtained: 115 slices, TR = 11.1ms, TE = 4.9ms, slice thickness = 1.4mm, FOV = 24 × 24 cm^2, FA = 20°.

Preprocessing of the functional data was performed with SPM8 package. The first ten volumes were discarded. Slice timing and realignment were performed to correct intra-volume and inter-volume head movement. Then, the functional images coregistered to the 3D-T1 images and normalized to the standard Montreal Neurological Institute (MNI) space. Finally, Resting-State fMRI Data Analysis Toolkit v1.7 [34], was used to remove the linear trend and for temporally band-pass filtering (0.01–0.08 Hz) the data, thus reducing the low-frequency drift