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Functional subdivisions of the hypothalamus using areal parcellation and their signal changes related to glucose metabolism

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ABSTRACT

The hypothalamus consists of numerous nuclei, and is regarded as the highest center for various autonomic functions. Although each hypothalamic nucleus implements a distinct function, it remains difficult to investigate the human hypothalamus at the nucleus level. In the present high-resolution functional MRI study, we utilized areal parcellation to discriminate individual nuclei in the human hypothalamus based on areal profiles of resting-state functional connectivity. The areal parcellation detected ten foci that were expected to represent hypothalamic nuclei, and the locations of the foci were consistent with those of the hypothalamic nuclei identified in previous histological studies. Regions of interest (ROI) analyses revealed contrasting brain activity changes following glucose ingestion: decrease in the ventromedial hypothalamic nucleus and increase in the lateral hypothalamic area in parallel with blood glucose increase. Moreover, decreased brain activity in the arcuate nucleus predicted future elevation of blood insulin during the first 10 min after glucose ingestion. These results suggest that the hypothalamic nuclei can putatively be determined using areal parcellation, and that the ROI analysis of the human hypothalamic nuclei is useful for future scientific and clinical investigations into the autonomic functions.

1. Introduction

The hypothalamus has been recognized as the highest-level center for autonomic functions (Kandel et al., 2013). Historically, the ventromedial nucleus of the hypothalamus (VMH) and the lateral hypothalamic area (LHA) act as a "satiety center" and a "feeding center", respectively (Hetherington and Ranson, 1940; Anand and Brobeck, 1951; Delgado and Anand, 1953; Miller, 1960). Recent investigations have revealed the arcuate nucleus (ARC) as a key structure regulating feeding behavior and energy homeostasis (Kubota et al., 2007; Williams and Elmquist, 2012; Sternson, 2013; Abraham et al., 2014; Krashes et al., 2016). The hypothalamus is also thought to modulate the release of insulin, a pancreatic hormone secreted in response to elevated blood glucose level (Ahrén, 2000; Teff, 2011; Chan and Sherwin, 2012). Even though the blood glucose level has not yet elevated, insulin is known to be secreted soon after food ingestion during the first 10 min (Berthoud et al., 1981; Bellisle et al., 1983; Teff et al., 1991; Ahrén, 2000). It has been reported that lesions to the hypothalamus enhance the insulin release (Louis-Sylvestre, 1976, 1978).

Most of the studies have been performed in rodents, and nucleus-level analysis of human hypothalamus remains relatively underinvestigated. Functional MRI (fMRI) has recently been utilized to investigate involvement of the human hypothalamus in energy homeostasis (Matsuda et al., 1999; Liu et al., 2000; Smeets et al., 2005; Batterham et al., 2007; Vidarsdottir et al., 2007; Teeuwisse et al., 2012; Page et al., 2013; Heni et al., 2014, 2015; Little et al., 2014; Jastreboff et al., 2016). It has been clarified that specific regions of the hypothalamus are associated with glucose metabolism. To further clarify the functional roles of the hypothalamus, it is important to segregate brain activity from the individual hypothalamic nuclei involved in distinct feeding and metabolic

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functions. Higher spatial resolution of the fMRI images and areal parcellation methods that determine hypothalamic nuclei will be useful in segregating brain activity from the hypothalamic nuclei.

Technological advancements in MRI have allowed us to apply high-resolution fMRI (Feinberg et al., 2010). Moreover, developments in resting-state functional connectivity (Fox and Raichle, 2007) and diffusion tractography (Le Bihan and Johansen-Berg, 2012) analyses have provided useful tools for the parcellation of the brain into various functional areas (Eickhoff et al., 2015). Areal parcellation using boundary mapping methods identify sharp changes in resting-state functional connectivity profiles as areal boundaries (Cohen et al., 2008; Biswal et al., 2010; Hirose et al., 2012, 2013, 2016; Wig et al., 2014a, 2014b; Laumann et al., 2015; Poldrack et al., 2015; Glasser et al., 2016). It has been demonstrated that the resting-state fMRI is more accurate in parcellation than other structural and functional features such as task-based fMRI, myelin maps or cortical thickness (Glasser et al., 2016). Moreover, resting-state functional connectivity has revealed region-specific patterns of connectivity between the hypothalamus and the cerebral cortex (Kullmann et al., 2014; Hirose et al., 2016). In the present study, high-resolution fMRI was applied to the hypothalamus to investigate glucose metabolism based on individual hypothalamic nuclei using the areal parcellation (Fig. 1A, Supplementary Fig. 1). During fMRI scans, human subjects drank glucose solution or water, and the plasma glucose, insulin and free fatty acid were sampled (Fig. 1B).

2. Materials and methods

2.1. Subjects

Twelve right-handed subjects [six males and six females, age: 26.6 ± 8.3 years (mean ± s.d.) ranging from 20 to 39] participated in the experiments. They were confirmed to be healthy by annual medical checkups. Written informed consent was obtained from all the subjects according to the Declaration of Helsinki. The body mass index (BMI) of the subjects was 21.6 ± 1.3 kg/m^2 (mean ± s.d.), ranging from 19.9 to 23.7. None of the subjects had been diagnosed with diabetes mellitus. The experimental procedures were approved by the Institutional Review Board of Juntendo University School of Medicine.

2.2. Experimental schedule

Subjects underwent two conditions: Glucose and Water conditions (Fig. 1B). The order of the two conditions was counterbalanced across subjects. Each condition consisted of two consecutive days of fMRI scanning (Day 1 and Day 2). Scanning on Day 1 was conducted in the evening, and scanning on Day 2 was conducted in the next morning following an overnight fast. During the Day 1 scanning, the subjects underwent task-free fMRI scans while resting quietly, and during the Day 2 scanning, the subjects drank glucose solution or water (Glucose or Water condition), while plasma glucose, insulin and free fatty acid were

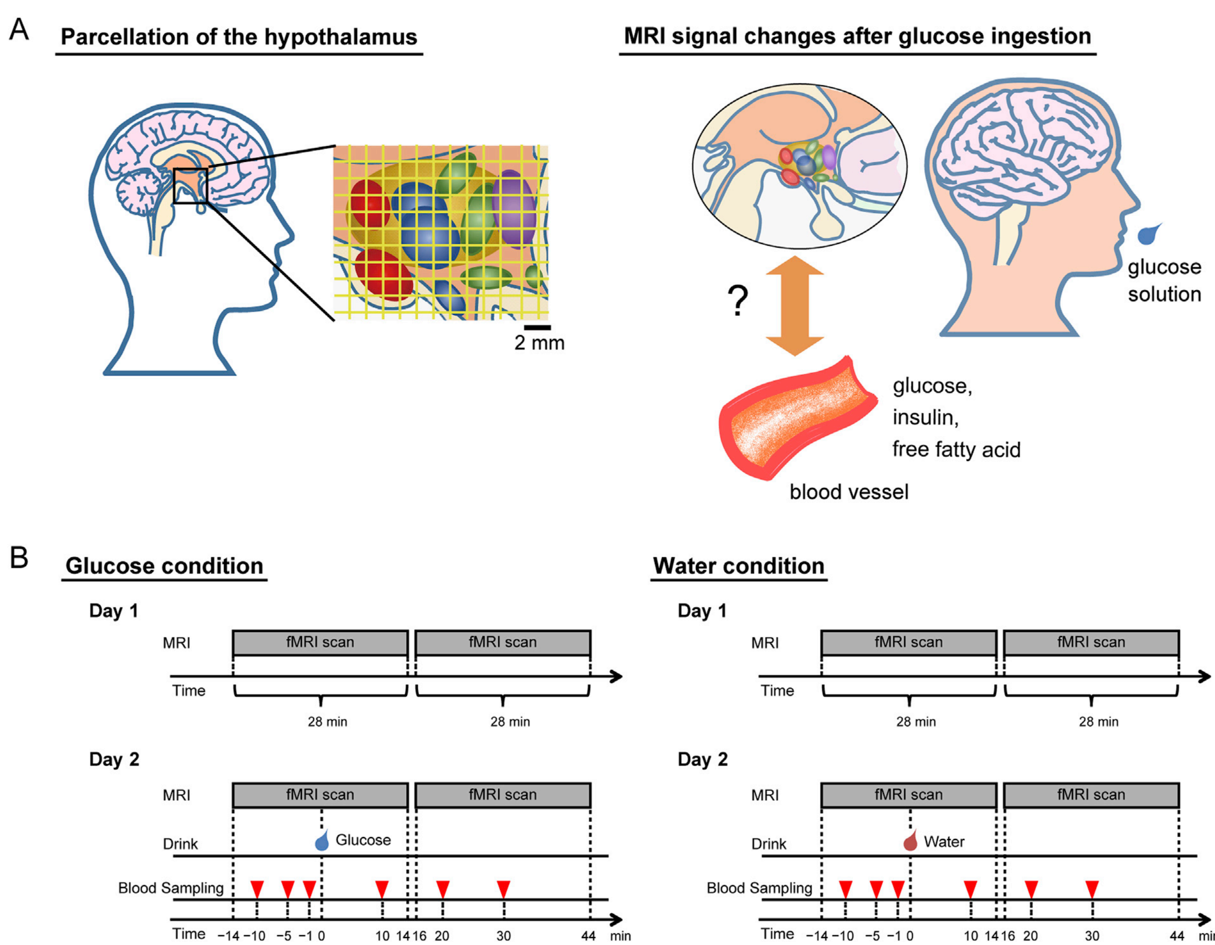

Fig. 1. Overview of the experiments. (A) The human hypothalamus was parcellated using high-resolution fMRI (1.25 mm voxel), and the associations between brain activity in each nucleus and blood levels of glucose, insulin, and free fatty acid were analyzed. (B) Subjects underwent two conditions: Glucose and Water conditions. Each condition consisted of two consecutive days of fMRI sessions: Day 1 and Day 2. During Day 1 scanning, the subjects underwent task-free fMRI scans, and during Day 2 scanning, the subjects drank glucose solution or water (Glucose or Water condition). Two runs of functional scans were acquired on both Day 1 and Day 2. On Day 2, blood samples were obtained inside the scanner at T = −10, −5, −1, 10, 20, and 30 min (the onset of drinking was defined as T = 0 min).