NeuroImage 69 (2013) 1–10

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Volumetric parcellation methodology of the human hypothalamus in neuroimaging: Normative data and sex differences

Nikos Makris [a,b,c,d], Dick F. Swaab [e], Andre van der Kouwe [d,f], Brandon Abbs [d,g,h,i,j], Denise Boriel [c,d], Robert J. Handa [k], Stuart Tobet [l], Jill M. Goldstein [a,d,g,h,i,j,*]

[a] Department of Psychiatry, Massachusetts General Hospital (MGH), 149 13th Street, Charlestown, MA 02129, USA
[b] Department Neurology, Massachusetts General Hospital (MGH), 149 13th Street, Charlestown, MA 02129, USA
[c] MGH Center for Morphometric Analysis, 149 13th Street, Charlestown, MA 02129, USA
[d] MGH & MIT Athinoula Martinos Biomedical Imaging Center, 149 13th Street, Charlestown, MA 02129, USA
[e] Department of Neuropsychiatric Disorders, Netherlands Institute for Neuroscience, an Institute of the Royal Netherlands Academy of Arts and Sciences, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands
[f] Department of Radiology, MGH, 149 13th Street, Charlestown, MA 02129, USA
[g] Brigham & Women's Hospital (BWH), Department of Psychiatry, 1620 Tremont St. BC-3-34, Boston, MA 02120, USA
[h] BWH, Department of Medicine, Division of Women's Health, Connors Center for Women's Health & Gender Biology, 1620 Tremont St. BC-3-34, Boston, MA 02120, USA
[i] Department of Psychiatry, Harvard Medical School, Boston, MA, USA
[j] Department of Medicine, Harvard Medical School, Boston, MA, USA
[k] Department of Basic Medical Sciences, University of Arizona College of Medicine, 425 N. Fifth Street, Phoenix, AZ 85004, USA
[l] Department of Biomedical Sciences, Colorado State University, 1680 Campus Delivery, Fort Collins, CO 80523, USA

ARTICLE INFO

Article history:
Accepted 1 December 2012
Available online 14 December 2012

Keywords:
Structural MRI
Volumetry
Hypothalamus
Hypothalamic nuclei
Tuberal region
Sex differences

ABSTRACT

There is increasing evidence regarding the importance of the hypothalamus for understanding sex differences in relation to neurological, psychiatric, endocrine and sleep disorders. Although different in histology, physiology, connections and function, multiple hypothalamic nuclei subserve non-voluntary functions and are nodal points for the purpose of maintaining homeostasis of the organism. Thus, given the critical importance of hypothalamic nuclei and their key multiple roles in regulating basic functions, it is important to develop the ability to conduct in vivo human studies of anatomic structure, volume, connectivity, and function of hypothalamic regions represented at the level of its nuclei. The goals of the present study were to develop a novel method of semi-automated volumetric parcellation for the human hypothalamus that could be used to investigate clinical conditions using MRI and to demonstrate its applicability. The proposed new method subdivides the hypothalamus into five parcels based on visible anatomic landmarks associated with specific nuclear groupings and was confirmed using two ex vivo hypothalami that were imaged in a 7 T (7 T) scanner and processed histologically. Imaging results were compared with histology from the same brain. Further, the method was applied to 44 healthy adults (26 men; 18 women, comparable on age, handedness, ethnicity, SES) to derive normative volumes and assess sex differences in hypothalamic regions using 1.5 T MRI. Men compared to women had a significantly larger total hypothalamus, relative to cerebrum size, similar for both hemispheres, a difference that was primarily driven by the tuberal region, with the sex effect size being largest in the superior tuberal region and, to a lesser extent, inferior tuberal region. Given the critical role of hypothalamic nuclei in multiple chronic diseases and the importance of sex differences, we argue that the use of the novel methodology presented here will allow for critical investigations of these disorders and further delineation of potential treatments, particularly sex-specific approaches to gene and drug discoveries that involve hypothalamic nuclei.

Introduction

Traditionally it has been difficult to assess hypothalamic involvement in specific human behavior, affect, and cognition, given the difficulties of measuring this structure in vivo. However, current studies using in vivo structural and functional magnetic resonance imaging (s/fMRI) in humans have demonstrated potential hypothalamic roles in mood and arousal (Augustinack et al., 2005; Bao et al., 2005; Goldstein et al., 2010, 2005; Handa et al., 1994; Majdic and Tobet, 2011), and psychiatric

* Corresponding author at: Brigham & Women's Hospital, One Brigham Circle, Division of Women's Health, 1620 Tremont St., 3rd Flr., Boston, MA 02120, USA. Fax: +1 617 525 7746.
E-mail addresses: nikos@cma.mgh.harvard.edu (N. Makris), d.f.swaab@nin.knaw.nl (D.F. Swaab), andre@nmr.mgh.harvard.edu (A. van der Kouwe), babbs@partners.org (B. Abbs), dlb@cma.mgh.harvard.edu (D. Boriel), rhanda@arizona.edu (R.J. Handa), Stuart.Tobet@colostate.edu (S. Tobet), jill_goldstein@hms.harvard.edu (J.M. Goldstein).

1053-8119/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neuroimage.2012.12.008

disorders (Goldstein et al., 2007). MRI offers advantages over traditional anatomy and histopathology, such as capabilities of in vivo measurement and monitoring of structure and function in healthy and clinical conditions. Using sMRI, a volumetric and topological analysis of the healthy hypothalamus with results matching those derived from traditional anatomy was used to differentiate schizophrenia patients, their first-degree relatives and healthy controls (Goldstein et al., 2007). Although this was an advance in the measurement and usefulness of the hypothalamus for understanding disease, there are a number of methodological and technological challenges that have hindered the progress of this line of research.

Anatomically, the human hypothalamus is a relatively small-sized structure, yet is considered a critical center for drive-related activities (such as feeding, defense and sexual behavior), endocrine and autonomic function (Baroncini et al., 2010; Saper et al., 2002; Swaab, 2003, 2004; Swanson, 2000). Currently, there is increasing evidence regarding the importance of the hypothalamus for understanding women's health and sex differences in relation to neurological, psychiatric, endocrine and sleep disorders. Although different in histology, physiology, connections and function, multiple nuclei of the hypothalamus subserve autonomic functions and are nodal points for the coordination of endocrine, emotional and somatic activities for the purpose of maintaining the organism within a healthy physiological equilibrium (i.e., homeostasis) (Saper et al., 2002; Swaab, 2003, 2004; Swanson, 2000). Overall, endocrine functions are primarily related to hypothalamic neuronal secretions into the median eminence to reach the anterior pituitary and direct projections to the posterior pituitary. Motivated behaviors are related to connections with limbic structures, such as the cingulate and parahippocampal gyri, amygdala and hippocampus. Somatic responses are associated with hypothalamic connections with somatic and visceral nuclei located within the brainstem and spinal cord (Koh and Ricardo, 1978; Saper et al., 2002). In fact, even specific nuclei within the hypothalamus, such as the paraventricular nucleus, have specific neuronal components associated with endocrine and autonomic functions (Herman et al., 2005; Stratton et al., 2011; Swaab, 2003, 2004; Swanson and Sawchenko, 1983). Hypothalamic regulation of the endocrine system plays a key role in the development of the sexual differentiation of the brain given the roles of hormones and genes on specific nuclei during particular gestational periods of development (Handa et al., 1994; Swaab, 2003, 2004; Tobet et al., 2009). This role has been demonstrated for many years in model animals and more recently in humans (Bao and Swaab, 2011; Goldstein et al., 2001; Raznahan et al., 2010). Thus, given the critical importance of hypothalamic nuclei and their key roles in regulating numerous functions, it is important to develop the ability to conduct in vivo human studies of anatomic structure, volumetry, connectivity, and function of hypothalamic regions represented at the level of its characteristic cell groups or nuclei. However, this level of structural analysis has not been currently achieved in hypothalamic MRI research. Traditional histology and immunohistochemistry has elucidated this level of analysis and thus serves as the “gold standard” to validate, guide and assist us in the MRI-based assessment and mapping of hypothalamic structure. Currently, the level of quantitative structural analysis that has been achieved in hypothalamic MRI research is measuring the volume of the entire hypothalamus using an approach of morphometric analysis (Goldstein et al., 2007). This is a different and complementary approach to the qualitative morphological characterization of the human hypothalamus for atlas generation using MRI (Baroncini et al., 2012).

The goals of the present study were two-fold: (1) develop a novel method of semi-automated, volumetric parcellation for the human hypothalamus that could be used to investigate clinical conditions using MRI, and (2) demonstrate the method's applicability. The new method extends previous work in which MRI was used to measure the entire hypothalamus as a single volumetric unit (Goldstein et al., 2007). In an effort to analyze quantitatively the human hypothalamus at a more fine-grained level, the new method subdivides the hypothalamus into five measurable parcels (or parcellation units [PUs]) based on visible anatomic landmarks that are associated with specific nuclear groupings. To validate this method, two ex vivo hypothalami were imaged at high resolution in a 7 T scanner and then processed histologically. Imaging results were compared with the histological evaluation. The parcellation methodology was then used to analyze the hypothalami from 44 healthy adult subjects (26 men; 18 women) to derive normative volumetric data and assess sex differences in the hypothalamus in its entirety as well as in its five subdivisions and thus infer associations with more specific hypothalamic nuclear groupings.

Methods

Anatomic parcellation of the human hypothalamus using MRI and its validation

The hypothalamus is located in the diencephalon, ventrally to the thalamus and hypothalamic sulcus and surrounding the third ventricle. It extends rostrally from the anterior commissure and the lamina terminalis to the ventral tegmentum caudally just behind the mamillary bodies. Its ventral surface is exposed to the subarachnoid space and the cerebral spinal fluid covering a distance from the optic chiasm to the caudal edge of the mamillary bodies (see Fig. 1). The hypothalamus is constituted by at least 13 nuclei, which have a specific topography and maintain characteristic topographic relationships among them (intrinsic connections) and their neighboring structures (extrinsic connections). Using histological and immunohistochemical techniques, the visualization of the nuclei is feasible. However, this is not currently possible using MRI given technological challenges such as spatial resolution. Thus to reliably segment the hypothalamus, it is necessary to follow conventions with respect to anatomic morphologic landmarks that consistently are identifiable using (Goldstein et al., 2007).

In the present method, the hypothalamus was first segmented as a whole in the coronal plane [as described by Goldstein et al. (2007)] using a semi-automated morphometric method based on 1.5-T MR images. Briefly, in the rostrocaudal dimension anteriorly, semi-automated segmentation of the hypothalamus began by convention at the coronal section containing the anterior-most tip of the anterior commissure (AC) and the optic chiasm (OC), which is reliable. The preoptic hypothalamus would be present on both sides of the third ventricle below the AC and above the OC. More caudally, at the level of the interventricular foramen of Monro and amygdala, the anterior part of the hypothalamus is observed on both sides of the third ventricle, and its lateral border at this level is demarcated by the lateral extent of the optic tracts as the optic chiasm bifurcates caudally. At a more caudal coronal level passing through the anterior thalamus, the amygdala and anterior hippocampus, the tuberal part of the hypothalamus is observed on each side of the third ventricle and segmented above the infundibular stalk and below the hypothalamic sulcus of Monro (Déjerine, 1895; Nieuwenhuys et al., 2008) and posterior limb of the internal capsule. Laterally, the hypothalamic border extends to the posterior limb of the internal capsule and the vicinity of the globus pallidus. Further caudally, the posterior part of the hypothalamus, including the mamillary bodies, is segmented. The lateral border of the hypothalamus is principally with the internal capsule, globus pallidus, and cerebral peduncle, whereas the medial border is at the midline of the hemisphere opposing the contralateral posterior hypothalamic nucleus and mamillary body. Its superior border is with the third ventricle and the diencephalic fissure. This border is prompted by white matter fibers above the mamillary body and lateral to the third ventricle, which belong principally to the mamillothalamic tract. The inferior border of the posterior hypothalamus is the hemispheric margin.

Subsequently, the hypothalamus was subdivided manually into five parcellation units (PUs) based on landmarks directly visible on