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Maps of the adult human hypothalamus

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Abstract

The human hypothalamus is a small deeply located region placed at the crossroad of neurovegetative, neuroendocrine, limbic, and optic systems. Although deep brain stimulation techniques have proven that it could be feasible to modulate these systems, targeting the hypothalamus and in particular specific nuclei and white bundles, is still challenging. Our goal was to make a synthesis of relevant topographical data of the human hypothalamus, under the form of magnetic resonance imaging maps useful for mastering its elaborated structure as well as its neighborhood. As from 1.5 Tesla, Inversion-Recovery sequence allows locating the hypothalamus and most of its components. Spotting hypothalamic compartments is possible according to specific landmarks: the anterior commissure, the mammillary bodies, the preoptic recess, the infundibular recess, the crest between the preoptic and the infundibular recesses, the optical tract, the fornix, and the mammillo-thalamic bundle. The identification of hypothalamus and most of its components could be useful to allow the quantification of local pathological processes and to target specific circuitry to alleviate severe symptoms, using physical or biological agents.

Key Words: Brain mapping, hypothalamus, inversion-recovery sequence, magnetic resonance imaging, stereotaxy

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INTRODUCTION

The hypothalamus is a small and heterogeneous region of the prosencephalon. It is situated in a strategic position at the crossroad of four systems, neurovegetative, neuroendocrine, limbic, and optic. Its numerous functional facets, from behavior to chronobiology, make the hypothalamus likely one of the most challenging region of the human brain. From a clinical perspective, several reports have proven that hypothalamus neuromodulation is possible;[10,12,23,26,33,34,50] however, the most important part of the clinical research has to be done before proposing reliable long-term invasive functional treatments. Paradoxically although the hypothalamus was extensively explored in several species, it is still a poorly known region of the deep human brain.

Pioneer's histological atlas provided details that are often difficult to relate to the clinical context. Our goal was to make a synthesis of relevant topographical data of the human hypothalamus, under the form of maps useful for mastering its elaborated structure. Magnetic resonance imaging (MRI) was used to create these maps, since it is the most advanced way to finely explore in a noninvasively the hypothalamus. This was accomplished using the widely available 1.5 Tesla device. Anatomical landmarks were defined to map structures to subject's peculiarities, providing means to further research protocols.

STRUCTURAL MRI ANATOMY OF THE HYPOTHALAMUS

The hypothalamus is a double diencephalic structure located within the right and left walls and the floor of the third ventricle. The pituitary stalk is developed from the infundibular recess to the hypophysis or pituitary gland. The hypothalamus is placed obliquely in front and below the thalamus, limited posteriorly by the subthalamus and the anterior upper brain stem [Figure 1].

Internal organization of hypothalamus

The adult's hypothalamus has a volume of approximately 0.7 cm^3 in each side, as measured on MRI.[43] It is composed of cellular heaps and white matter fibers. The cellular heaps form nuclei, which are regrouped in regions and zones,[15] according to topographic and cytoarchitectural organization.

The visualization of all hypothalamic nuclei and white matter tracts is not feasible with current clinical imaging; however, several pertinent landmarks are identifiable with 1.5 Tesla using appropriate sequences.[13] T1-weighted images allow recognizing the overall morphology of walls and floor of the third ventricle, as well as the fornix and the mammillary bodies Moreover, inversion-recovery sequences[36,44] enhance the contrast between white and gray matters, allowing identifying basal ganglia, thalamus and hypothalamus, as well as white matter structures [Figure 2].

The complex organization of hypothalamic nuclei makes it difficult to visualize details of location and shape of the nuclear heaps. However, it can be made simpler using semi-realistic drawing[43] and 3D reconstruction[32] [Figure 3].

Most hypothalamic nuclei are well described, however, there are still ambiguous definitions revealing the incomplete understanding of each nucleus in humans.[15,43] The group of preoptic nuclei, also named prothalamus, is the most rostral; it contains the medial and lateral preoptic nuclei and the anterior nucleus. Behind, medial and superficial, lies the thin paraventricular nucleus, placed just under the wall of the third ventricle. This

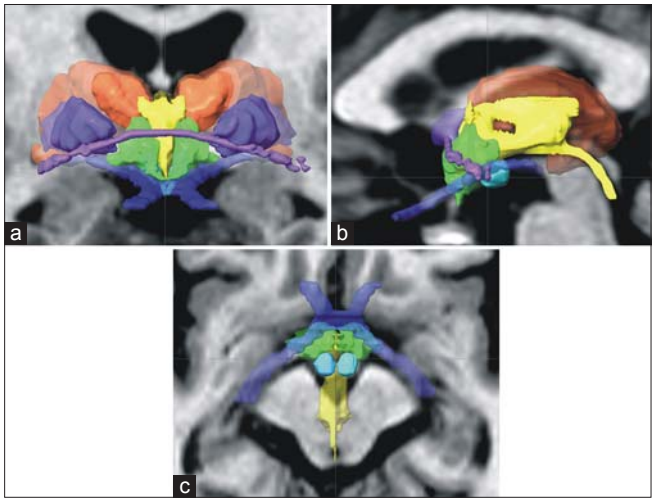

Figure 1: 3D reconstruction of the adult human hypothalamus displayed on three orthogonal (a. Frontal view; b. Left lateral view; c. Inferior view) T1-weighted MRI slices crossing the mammillary bodies (light blue): hypothalamus (green plus light blue), anterior white commissure (purple), thalamus (brown), pallidum (purple), third ventricle (yellow; the brain aqueduct and the ventricular foramen are also reconstructed), and optical system (dark blue)

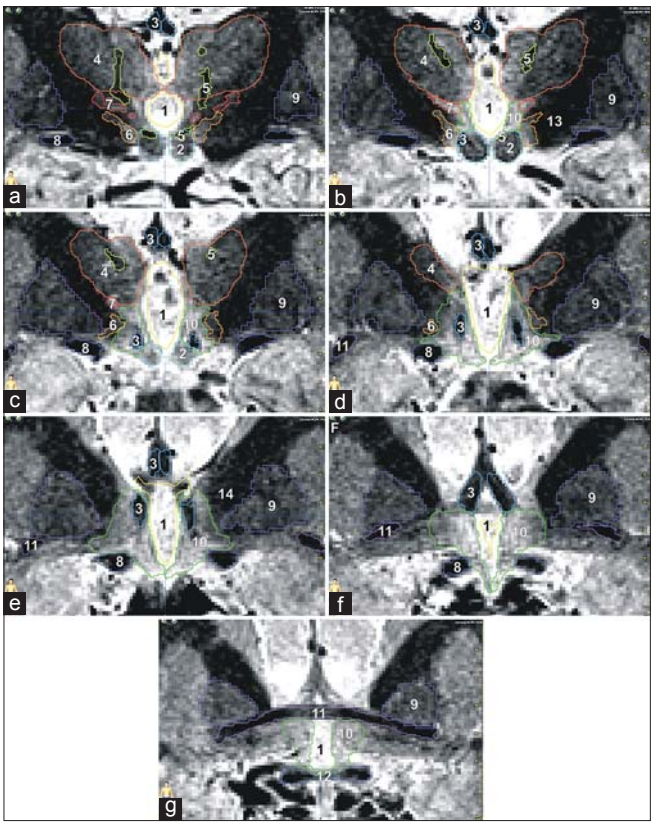

Figure 2: MRI coronal slices (white matter attenuated inversion recovery sequence; joined slices, matri × 0.56 × 0.56 mm, 2-mm thickness) from posterior (a) to anterior (g): third ventricle (1), mammillary body (2), fornix (3), thalamus (4), mammillo-thalamic bundle or Vicq d'Azyr fascicle (5), nucleus entopedoncularis or nucleus of ansa lenticularis (6), zona incerta (7), optical tract (8), pallidum (9), hypothalamus (10), anterior white commissure (11), optic chiasma (12), internal capsule posterior limb (13), internal capsule anterior limb (14)

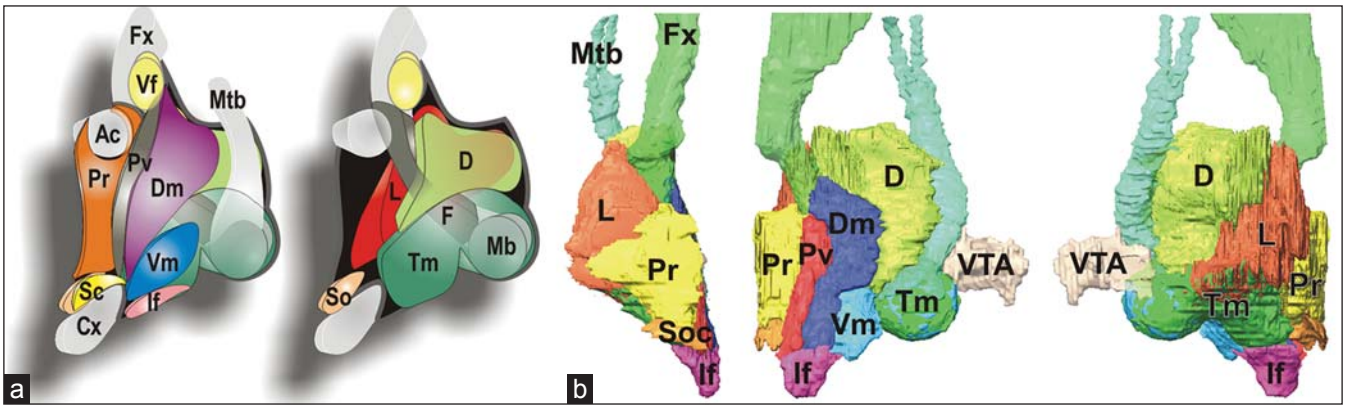

Figure 3: (a) Schematic drawing of hypothalamic nuclei, lateral view from the midline; left, nuclei directly located under the wall of the third ventricle; right, more deeply located nuclei up to the lateral region. (b) 3D overview of hypothalamic nuclei, constructed from a 3D high-field MRI data set; left, frontal view; intermediate, lateral view; right, medial view; the ventral tegmental area (VTA) is located within the retro hypothalamic region. Anterior commissure, Ac; dorsal or posterior nucleus, D; dorsomedial nucleus, Dm; fornix, Fx; fornix nuclei F; infundibular (arcuate) nucleus, If; lateral nucleus, L; mammillary body, Mb; mammillo-thalamic bundle, Mtb; optic chiasma, Cx; paraventricular nucleus, Pv; preoptic nuclei, Pr; suprachiasmatic (ovoid) nucleus, Sc; ventricular foramen, Vf; supraoptic (tangential) nucleus, So; tuberomamillaris (mamilloinfundibularis) nucleus, Tm; ventromedial (tuber principal) nucleus, Vm

latter can also be regrouped with the preoptic group, as well as lateral sparse cells belonging to the lateral nucleus. The supraoptic nucleus and the suprachiasmatic nucleus, respectively, lateral and medial, are placed under the preoptic group, above the optical tract. The most caudal nuclei of the hypothalamus are those related to the mammillary bodies, that is, lateral, medial, premamillary, and supramamillary nuclei. The dorsal or posterior nucleus is limited caudally by the mammillo-thalamic bundle. It is located mainly above the tuberomamillaris nucleus. The lateral nucleus is the most lateral hypothalamic nucleus, lying from rostral to caudal; it borders the tuberomamillaris nucleus located more ventrally and medially. The boundary between the tuberomamillaris nucleus and the lateral nucleus is not precise. Directly medially to the lateral nucleus is the group of nuclei belonging to the fornix. The medial nuclei of the hypothalamus are the dorsomedial and the ventromedial nuclei, which are, respectively, anterior or rostral, and posterior. The most antero-ventral nucleus is the infundibular or arcuate nucleus, located behind the optic chiasma; it forms the anterior wall of the infundibulum. The so-called posterior hypothalamus is a poorly defined region, more related to the upper and anterior part of the mesencephalon; it is better known as the ventral tegmental area (VTA) or area densa, which neighbors the entopedoncularis nucleus or ansa lenticularis nucleus.[32] Finally, the periventricular zone is a wide region located just under the wall of the third ventricle, extended from anterior to posterior, where lie the paraventricular nucleus and the posterior periventricular nucleus or hypothalamic periventricular zone.[59]

Hypothalamus neighborhood

The anatomic relationships are numerous and can be regrouped according to three main structures of each hemisphere, the subcallosal area of the limbic lobe[1] of the limbic system, the basal ganglia, and the thalamus. The elements of basal ganglia neighboring the hypothalamus are the striatum, the medial pallidum, the substantia innominata, and the ansa lenticularis nucleus. The ansa lenticularis nucleus runs along the medial border of the projection fibers of the posterior limb of the internal capsule, bridging the sublenticular region with the subthalamus up to the red nucleus (see for an overview of anatomic terminology). The closest neighbors of the hypothalamus, belonging to the thalamus, are the anterior thalamic nuclei, and the superficial reticular layer or reticular nucleus. The connections between thalamic nuclei and hypothalamus follow the inferior thalamic peduncle, the mammillo-thalamic bundle and the stria medullaris; this latter connects the hypothalamus with the habenula or epithalamus. The main white matter tracts connected with the hypothalamus are: The fornix extending to the fimbria, the stria terminalis that connects the amygdala, the stria medullaris, the fascicle olfactorius or diagonal band of Broca, the anterior thalamic peduncles, the supraoptic commissure, the ansa lenticularis, the basal forebrain bundle, the mammillo-tegmental tract, and the radiate system going through the deep brain toward the cortex.[43] The internal capsule composed of white matter tracts, lines the hypothalamus laterally from the anterior limb to the posterior limb [Figure 2], as well as the sublenticular limb that contains in particular the ansa lenticularis.[39]

Figure 4 summarizes most of the structures neighboring the hypothalamus.

MRI spotting of the hypothalamus

The location of human hypothalamus and hypothalamic nuclei have been studied;[2,3,7,8,15,16,21,29,31,35,38,45,49,52,59] including stereotactic spotting.[4,35,38] Recently, a relative mapping using local MRI landmarks has been proposed, enabling

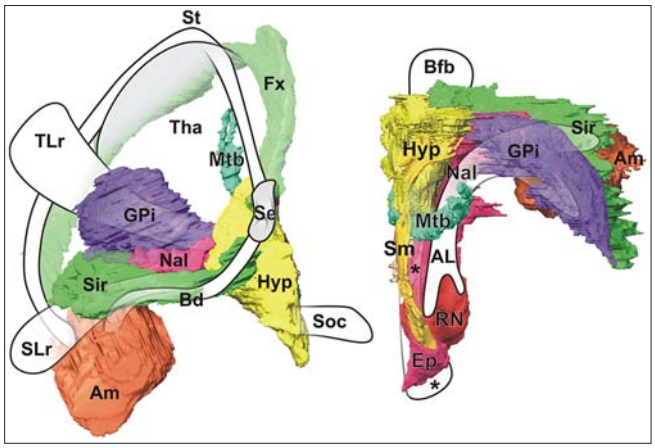

Figure 4: Overview of structures neighboring the hypothalamus (Hyp), 3D reconstruction from a high-field MRI data set merged with schematic drawing; left, frontal view; right, superior view: amygdala, Am; ansa lenticularis nucleus, Nal; basal forebrain bundle, Bfb (and *); diagonal band of Broca, Bd; epithalamus, Ep; fornix, Fx; globus pallidum intern, GPi; mammillo-thalamic bundle, Mtb; red nucleus, RN; septum, Se; stria medullaris, Sm; stria terminalis, St; sublenticular radiations, SLr; substantia innominata (of Reichert), Sir; translenticular radiations, TLr; supraoptic commissure, Soc; thalamus, Tha

the study of the macro connectivity of the hypothalamus. The diagram of six hypothalamic compartments is built from MRI remarkable points: The anterior commissure, the mammillary bodies, the preoptic recess, the infundibular recess, the crest between the preoptic and the infundibular recesses, the optical tract, the fornix and the mammillo-thalamic bundle; see Figures 5 and 6 for details. This approach allows a personalized exploration of the hypothalamus, its nuclei and the main white matter bundles, for each individual, whether patient or healthy subject.

THERAPEUTIC PERSPECTIVES

The anatomo-functional architecture of the hypothalamus is well-established;[15,59] however, the small size of the structure, that is, of its components, nuclei and white matter tracts, makes the development of a clinical, macro- or mesoscopic functional systematization challenging. As mentioned before, the hypothalamus is at the crossroads of neurovegetative, neuroendocrine, limbic, and optic systems, which are deeply intricate. Three examples were selected from a therapeutic perspective to illustrate the challenge of selective neuromodulation of a specific functional system with chronic electric stimulation well-known as deep brain stimulation (DBS).[28,54]

Visual system and hypothalamus

The retino-hypothalamus tract (RHT) is the main connection between the eye and the hypothalamus, a direct afferent pathway from the retina, going through the optic chiasma. In mammalians, axons of photosensitive

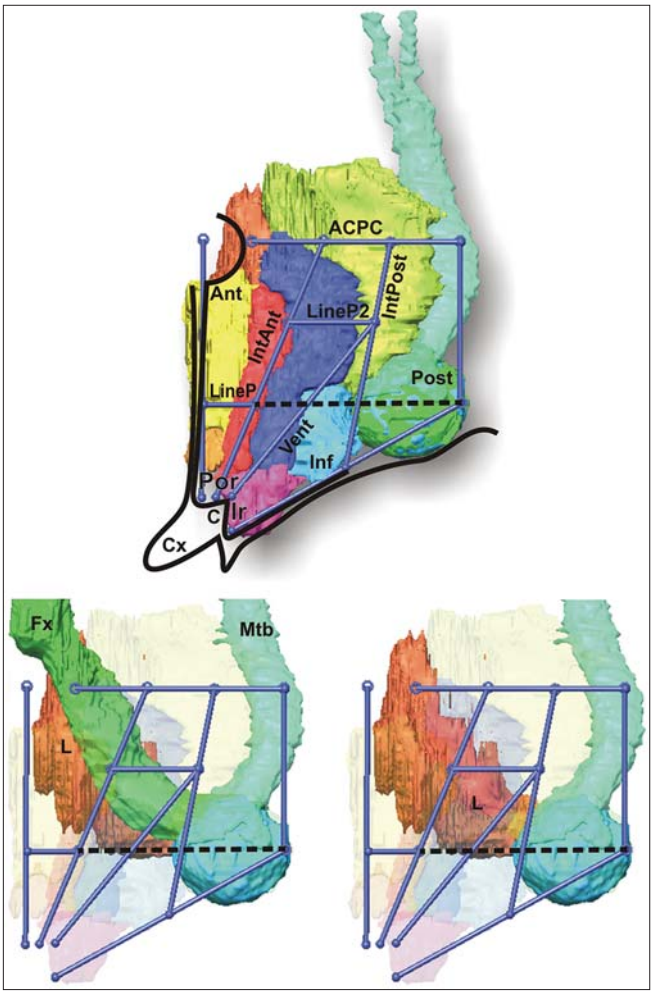

Figure 5: MRI landmarks and line used to spot hypothalamic compartments and nuclei (projection on 3D reconstruction from a high-field MRI data set; lateral view. (a) The hypothalamus is lined posteriorly by the vertical line (Post) placed behind the mammillary body and perpendicular to an anterior commissure posterior commissure (ACPC) segment. The anterior line (Ant) rises from the preoptic recess (Por), perpendicular to ACPC. Two intermediate lines, anterior (IntAnt) and posterior (IntPost), respectively, goes from the dorsal region of the optic chiasma (Cx) to the anterior point of the intermediate third of the ACPC line and from the crest (c) placed between the optical recess and the infundibular recess (Ir), to the posterior point of the intermediate third of the ACPC line. The anterior horizontal line (LineP; doted black line) goes parallel to ACPC (toward the posterior point at the origin of Post). The intermediate horizontal line (LineP2) is parallel to ACPC and origins at the midpoint of the segment of IntAnt between the point where IntAnt crosses LineP and the point where IntAnt crosses ACPC. The ventral line (Vent) goes from C to the intersection of LineP2 and IntPost. (b) The fornix limits the medial border of the lateral nucleus (l), which is visible in the background; the mammillo-thalamic bundle (Mtb) is displayed. (c) The area limited by the LineP2, LineP and IntAnt and IntPost projects on the lateral nucleus

retinal ganglion cells, expressing melanopsin, project to the suprachiasmatic nucleus.[22,30,37,57] Retinal projections to nonvisual centers have been identified in animals, with equally crossed and uncrossed hypothalamic fiber that represent 5% of retinal fibers;[18,25,46,47] the axonal

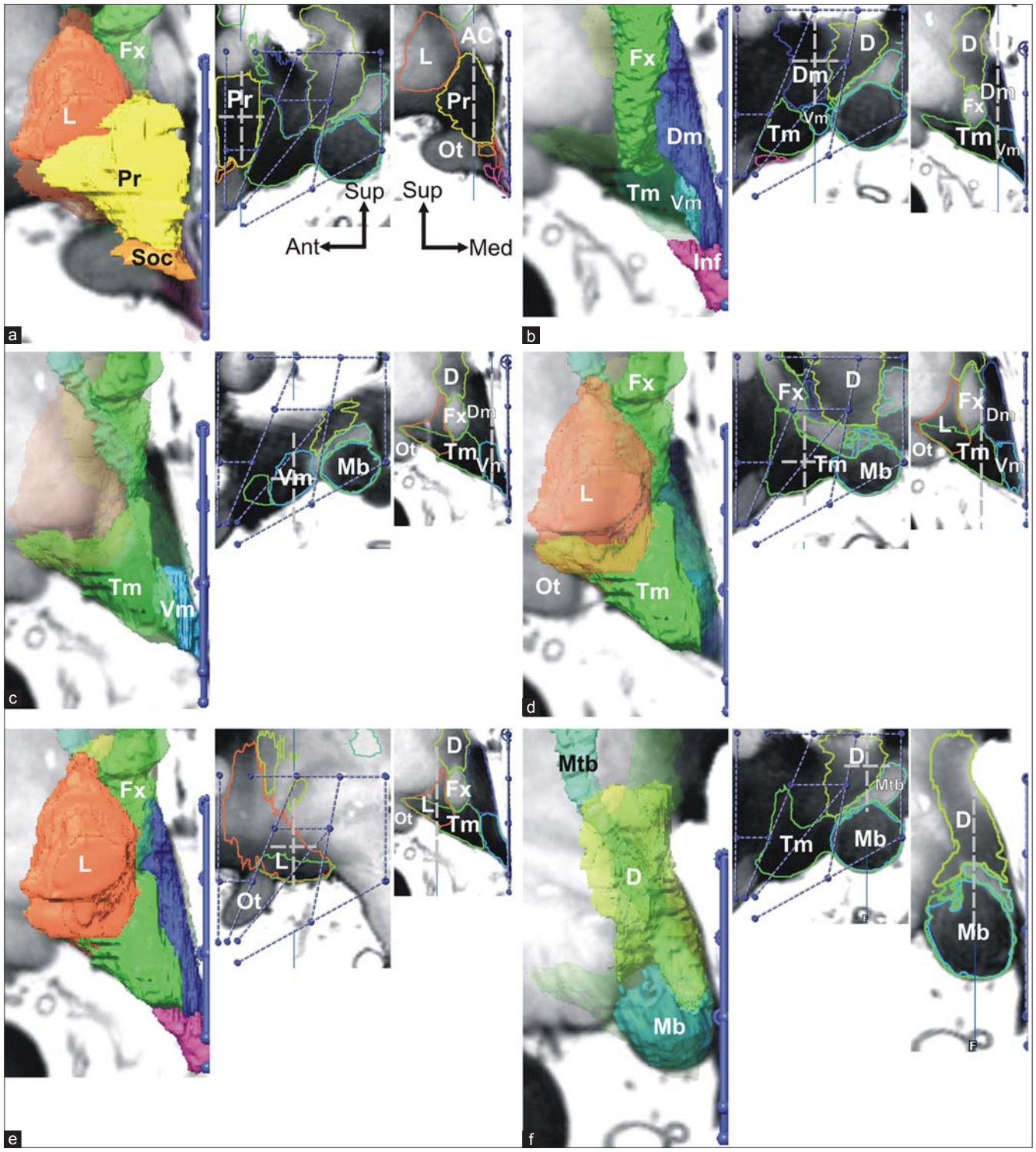

Figure 6: MRI landmarks and lines used to spot hypothalamic compartments and nuclei (projection on 3D reconstruction from a high-field MRI data set. From A to F: left, frontal view; intermediate, sagittal slice, right, coronal slice; gray dotted lines show section plans. (a) Preoptic nuclei (Pr) and supraoptic plus suprachiasmatic nuclei (Soc). (b) Dorsomedial nucleus (Dm) lined laterally by the fornix. (c) Ventromedial nucleus (Vm) lined laterally by the tuberomamillaris nucleus (Tm). (d) Tuberomamillaris nucleus (Tm); placed below the fornix extending laterally to the optical tract (Ot). (e) Lateral nucleus (l), lined medially by the fornix; the inferior region overlaps with the tuberomamillaris nucleus. (f) Dorsal nucleus (d), placed behind the fornix (not visible here) and lined posteriorly by the mammillo-thalamic bundle (Mtb)

targets are the following hypothalamic nuclei: The supra chiasmatic nucleus, the supra optic nucleus, and the sub periventricular area; the olivary pretectal nucleus, the intergeniculate leaflets of the geniculate nuclei, the medial amygdala, the lateral habenula, the nucleus posterior limitans of the thalamus, the superior colliculus

and the periaqueductal gray. Sadun and Schaechter[20,41] described first in human the RHT, which penetrates the hypothalamus into the suprachiasmatic nucleus, ending locally and in the paraventricular nucleus.[9] The suprachiasmatic nucleus is well-known as the hypothalamic clock,[42] synchronizing several biorhythms such as sleep-arousal and food intake; in rats the ventromedial and the lateral nuclei also have circadian rhythms.[19]

Limbic system and hypothalamus

Two groups of hypothalamic nuclei are directly involved in the limbic circuitry, the preoptic and the mammillary. Broadly the preoptic connects the frontal lobe, the thalamo-tegmental region, the septum, the lenticular nucleus, the substantia innominata of Reichert, and the anterior perforate; mainly through the basal forebrain bundle, the ansa lenticularis, and the radiate system; the medial nucleus of the preoptic nucleus being in continuity with the nucleus of the stria terminalis.[35] The mammillary nuclei participate to the limbic circuitry through the fornix and the mammillo-thalamic bundle. The fornix emerges from the hippocampus and terminates anteriorly and laterally, into the ipsilateral mammillary body; the precommissural fornix could be continuous with the diagonal band of Broca.[3,21] The mammillo-thalamic bundle terminates into the ipsilateral anterior nucleus of the thalamus, from which neuronal relays go to the cingulum.[3,51]

From a white matter tract point of view, the stria medullaris of the thalamus connects the epithalamus or habenula, with the preoptic and septal regions, and also possibly with the nucleus of Meynert.[3,40] The basal forebrain bundle, bidirectional, links the upper brain stem, mostly the tegmentum with the anterolateral hypothalamus, the olfactory region, the septum, the nucleus accumbens, the amygdala, and the substantia innominata of Reichert.[21,53] The diagonal band of Broca connects the septal region, the anterior perforate region and the olfactory area with the amygdala, and possibly the lateral hypothalamus.[3,21] In rats, hypothalamic stimulation enhances hippocampal plasticity.[3,21] In humans, DBS of the lateral hypothalamus close to the fornix seems to improve memory processing.[23,50]

Appetite control and hypothalamus

The hypothalamus is a major integrator of hormonal and nutrient-induced signals of hunger and satiety with the aim of regulating energy stores and food intakes. The central role of the hypothalamus in the control of feeding has emerged in the past century from lesioning studies. Indeed, various lesions of the ventromedial hypothalamus were shown to cause hyperphagia and obesity[6] while lesions of the lateral hypothalamus caused reduced food intake and leanness.[27] These studies indicated that key hypothalamic areas activate responses to promote negative energy balance (i.e., reduced food intake and increased energy expenditure) and decreased nutrient availability (reduced endogenous glucose production). Accordingly, impaired responses or a sort of resistance to afferent input from these hormonal or nutrient-related signals would be predicted to favor weight gain and insulin resistance and may contribute to the development of obesity and type 2 diabetes.[17] Many reports have been focused on the identification of hypothalamic pathways that control energy but recent evidence suggests, however, that in addition to playing a critical role in the regulation of energy homeostasis, the central nervous system also control peripheral metabolisms such as glucose metabolism via hypothalamic sensors detecting nutrients availability.

Mechanisms of appetite control became a public health focus because of its numerous clinical implications of obesity, currently reaching world epidemic levels.[56] Weight loss is one of the main therapeutic goals to decrease the related morbidity and mortality of obesity. Therefore, morbidly obese subjects (body mass index >40 kg/m^2) are more and more subjected to bariatric surgery. The highly invasive end mutilating nature of bariatric surgery and its long-term frequent failure limits its use to patients who failed intense medical management. Common side effects of bariatric surgery include poorly understood digestive changes, which are not well-tolerated by the patients. They tend to eat small and repeated meals to compensate for the fact that mal absorption and sense of fullness main the state of hunger. This leads to higher energy intakes and regain weight.[14]

The neurobehavioral aspects of obesity are complex and poorly understood, food sensing and craving are currently major areas of research. The neurologic component of food regulation is centered on the hypothalamus.[58] Recently, functional changes in brain activities in response to food have been seen in humans by using functional magnetic resonance imaging (fMRI).[55] These data emphasize the major regulatory action of central metabolic sensing in the regulation of body weight, however, the modifications of brain structure and function during morbid obesity are still poorly realized. Recently, Thaler *et al.*[11] reported hypothalamic lesions associated with obesity that could impact the efficiency of DBS. Five hypothalamic nuclei are known to be involved in appetite control.[5,10,24,48]: The lateral nucleus, the ventromedial and dorsomedial nuclei, the paraventricular nucleus and the arcuate or infundibular nucleus. Although clinical benefit of chronic electric stimulation of lateral hypothalamus is still unproved in humans,[50] recent animals studies have demonstrated weight control using electric modulation of the ventromedial nucleus.[5,10,24,26] Studies of the hypothalamic stimulation to control food intake failed to control a patient's weight but suggested the perifornixial stimulation may improve memory processing.[23,50]

CONCLUSION

Involved on human neurological function such as memory, neurovegetative, neuroendocrine, behavior, and chronobiological rhythms, the human hypothalamus emerges as the next challenging human structure to understand and modulate in the next decades. The advances of functional and anatomical images, including positron emission tomography, high tesla MRI and the modern computational ability to integrate these images to enhance our understanding of functional localization in the hypothalamus, likely will open up a new therapeutic frontier based on physical and biological agents to treat ailments yet not reached by our modern medicine.

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