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BRAIN RESEARCH

Research Report

White matter connectivity of human hypothalamus

Jean-Jacques Lemaire^{a,b,*}, Andrew J. Frew^{b,e}, David McArthur^b, Alessandra A. Gorgulho^b, Jeffry R. Alger^{c,e}, Noriko Salomon^d, Clive Chen^b, Eric J. Behnke^b, Antonio A.F. De Salles^b

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ABSTRACT

The macroscopic extrinsic white matter connectivity and the internal structure of the hypothalamus are still incompletely defined in humans. We investigated whether in-vivo diffusion tensor imaging tractography provides evidence of systematization according to hypothalamic compartmentalization. Six defined hypothalamic macroscopic compartments, preoptic, supraoptic, anteroventral, anterodorsal, lateral and posterior, were probed, within the right and left hemispheres of 14 subjects. Important new insights into the macroscopic structure of hypothalamus and white matter connections were found; the preoptic, anteroventral, lateral and posterior compartments are strongly connected to the cortex. The anteroventral connects particularly to the prefrontal cortex while the preoptic compartment connects mainly to the deep anterior brain. The anterodorsal connects mainly to the medial thalamus and the midline gray matter. There is a rightward frontal trend of hemispheric connectivity for the preoptic, anteroventral and lateral compartments. These findings may aid new neuromodulation applications and understanding in brain connectomics.

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Glossary

The human hypothalamus is a multi-nuclear anatomic structure located below and anteriorly to the thalamus and crossed by the basal forebrain bundle. It is placed medially to the basal ganglia and the anterior limb of the internal capsule. The macroscopic boundaries are: rostrally the lamina terminalis and the preoptic region (confounded with hypothalamus); caudally the mamillary region and the posterior or dorsal hypothalamic nucleus (this latter being

contiguous with the central gray matter); laterally the internal capsule and the substantia innominata of Reichert; and medially the wall of the third ventricle (Haymaker et al., 1969). The ventral and anterior part of the third ventricle, or infundibulum, is also named as the median eminence viewed from the base of the brain. The posterior hypothalamus is a topographic region poorly defined in humans (Fontaine et al., 2010) where Schaltenbrand and Wahren, 1977 identified a small region named the post mamillary hypothalamus. It is likely that this confined region belongs to

^aUniv Clermont 1, UFR Médecine, EA3295, Equipe de Recherche en signal et Imagerie Médicale, Clermont-Ferrand, F-63001, France

^bDepartment of Neurosurgery, University of California, Los Angeles, USA

^cDepartment of Neurology, University of California, Los Angeles, USA

^dDepartment of Radiology, University of California, Los Angeles, USA

^eHuman Brain Mapping Center, University of California, Los Angeles, USA

^{*} Corresponding author. Service de Neurochirurgie A, Hôpital Gabriel Montpied, B.P. 69, 63003 Clermont-Ferrand cedex 1, France. Fax: +33 4 73 75 21 66.

E-mail address: jjlemaire@chu-clermontferrand.fr (J.-J. Lemaire).

the continuous gray matter territory between the substantia innominata of Reichert and the subthalamus (see substantia innominata of Reichert and ventral tegmental area).

- Ansa lenticularis and ansa peduncularis: The ansa lenticularis (bidirectional connection) connects the amygdalo-pyriform complex to the lateral hypothalamus, up to the mediodorsal nucleus (Riley, 1953; Nauta and Haymaker, 1969). The ansa peduncularis consists of the ansa lenticularis plus the inferior thalamic peduncle (Riley, 1953; Nieuwenhuys et al., 1979) and connects the medial thalamus, the subthalamus, the hypothalamus, with the temporal (medial) and frontal (orbital) lobes. Practically, the ansa lenticularis, in its wide meaning, includes all the fiber bundles connecting the thalamo-subthalamic region with the sublenticular region; fibers are deployed from the postero-medial region of the deep brain toward the lateral (temporal), and at a lesser extent anterior (frontal) brain.
- Basal (or medial) forebrain bundle: The basal forebrain bundle fills almost the entire lateral region of hypothalamus. It mainly connects the lateral part of the pre hypothalamus with the upper brain stem, mostly the tegmentum (Nauta and Haymaker, 1969; Palkovits and Zaborszky, 1979). It is a bidirectional connection formed of loose-textured bundles of aminergic tracts (noradrenergic, in particular from the locus coeruelus; dopaminergic, in particular from the ventral tegmental area; adrenergic; serotoninergic; histamine; and choline). The rostral origin of the basal forebrain bundle is multiple: the olfactory region, septum, nucleus accumbens, the amygdala and the substantia innominata of Reichert (Nauta and Haymaker, 1969; Palkovits and Zaborszky, 1979).
- Fascicle olfactorius: The fascicle olfactorius or diagonal band of Broca connects the septal region, the anterior perforate region and the olfactory area with the amygdala, and possibly the lateral hypothalamus; the fascicle olfactorius seems to be continuous with the pre commissural fornix (or fornix longitudinal) (Riley, 1953; Nauta and Haymaker, 1969).
- Fornix: The columns of the fornix receive, en passant, fibers from the anterior and middle hypothalamus, before terminating within the mamillary body (lateral). Hypocampic fibers join the medial hypothalamus taking the medial corticohypothalamic tract lining the fornix.
- Periventricular (or periependymal) tracts: These tracts connect
 the hypothalamus with the substantia grisea (midline gray
 substance) of the mesencephalon and of the third ventricle
 and the thalamus (medial and midline groups of nuclei)
 (bidirectional aminergic pathway). They belong to the wall
 of the third ventricle and a dorsal division is named the
 dorsal longitudinal fascicle (Riley, 1953; Palkovits and
 Zaborszky, 1979; Palkovits and Zaborszky, 1979).
- Stria terminalis (or semi cicularis): The stria terminalis
 connects the amygdala with the preoptic and septal areas
 the pre hypothalamus, the dorso and ventromedial nuclei
 and the suprachiasmatic nucleus (Riley, 1953; Nauta and
 Haymaker, 1969; Palkovits and Zaborszky, 1979). In rat the
 ventrolateral bed nucleus of the stria terminalis receives
 input from the medial preoptic area, perifornical, arcuate,

- dorsomedial and posterior hypothalamic nuclei (Shin et al., 2008).
- · Substantia innominata (of Reichert): The labels of the gray matter territories belonging to the sub striato-pallidal region are not precise and the term substantia innominata have become an anachronism (Heimer et al., 1997). However because it is still common, it was used in the manuscript. It seems that there is a mostly cholinergic medial component, the nucleus basalis of Meynert (Perry et al., 1984; Heimer et al., 1997). The substantia innominata is also named the nucleus ansa lenticularis when merging with the ans lenticularis, or the nucleus entopeduncularis when penetrating the subthalamus (Riley, 1953). The lateral ("hypolenticularis") part is often named the nucleus of the dorsal supraoptic commissure of Meynert (Riley, 1953; Naidich et al., 2009). However the term nucleus basal and substantia innominata are often merged and correspond to other terms: nucleus ansa lentiformis, nucleus praeopticus magnocellularis and basal ganglion (Schaltenbrand and Bailey, 1959).
- Stria medullaris (of the thalamus): This bundle mainly connects the epithalamus (habenula) with the preoptic and septal regions, but the habeno-hypothalamic connectivity is still doubtful; it connects also possibly the habenula with the nucleus of Meynert and the hypothalamus (Riley, 1953; Palkovits and Zaborszky, 1979).
- Supraoptic commissures (or decussations): Three groups of fibers (Ganser's, Meynert's and Gudden's) connect (from the shortest fibers to the longest), the hypothalamus, the substantia innominata (pars lateralis), the pallidum, the subthalamus, the lateral geniculate body, the tectum and tegmental ascending aminergic area (Riley, 1953; Palkovits and Zaborszky, 1979, 1979). The most dorsal, the Ganser's commissure connects the two hypothalamus.
- The ventral tegmental area: This upper brain stem region corresponds to the A10 dopamine nucleus of several species that project, with neurons of the substantia nigra compacta, to the striatum, the forebrain and the lateral hypothalamus (Ikemoto, 2007); however the nuclei also contains GABAergic and glutamatergic neurons (Fields et al., 2007). In humans it corresponds to the medial and anterior region of the cerebral peduncle, in front of the red nucleus and medially to the substantia nigra. The ventral tegmental area likely corresponds to the area densa and the nucleus entopeduncularis belonging to the continuous band of islands of neurons located between the subthalamus and the substantia innominata of Reichert (Riley, 1953; Fontaine et al., 2010).

1. Introduction

The hypothalamus and its functions have been extensively explored in various species anatomically, histologically and physiologically (see Riley, 1953; Haymaker et al., 1969; Schaltenbrand and Wahren, 1977; Morgane and Panksepp, 1979; Saper, 2004; Card, 2009; Young and Stanton, 1994; Page, 2006; Card and Rinaman, 2002; Swaab, 1997; Mai and Ashwell, 2004; Koutcherov et al., 2003; Toni et al., 2004, for a review). However the anatomy of the human hypothalamus, in

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