TECHNICAL WHITE PAPER:
ONTOLOGY AND NOMENCLATURE

OVERVIEW

Currently no “standard” anatomical ontology is available for the description of human brain development. The main goal behind the generation of this ontology was to guide specific brain tissue sampling for transcriptome analysis (RNA sequencing) and gene expression microarray using laser microdissection (LMD), and to provide nomenclatures for reference atlases of human brain development. This ontology also aimed to cover both developing and adult human brain structures and to be mostly comparable to the nomenclatures for non-human primates. To reach these goals some structure groupings are different from what is traditionally put forth in the literature. In addition, some acronyms and structure abbreviations also differ from commonly used terms in order to provide unique identifiers across the integrated ontologies and nomenclatures.

This ontology follows general developmental stages of the brain and contains both transient (*e.g.*, subplate zone and ganglionic eminence in the forebrain) and established brain structures. The following are some important features of this ontology. First, four main branches, *i.e.*, gray matter, white matter, ventricles and surface structures, were generated under the three major brain regions (forebrain, midbrain and hindbrain). Second, different cortical regions were named as different “cortices” or “areas” rather than “lobes” and “gyri”, due to the difference in cortical appearance between developing (smooth) and mature (gyral) human brains. Third, an additional “transient structures” branch was generated under the “gray matter” branch of the three major brain regions to guide the sampling of some important transient brain lamina and regions. Fourth, the “surface structures” branch mainly contains important brain surface landmarks such as cortical sulci and gyri as well as roots of cranial nerves. Finally, nomenclature for some regions or subregions was slightly modified based on recent literature.

ONTOLOGY AND NOMENCLATURE OF SPECIFIC BRAIN REGIONS

Cerebral cortex

In this ontology, the cerebral cortex was subdivided into three major categories mainly based on Filimonoff (1947): allocortex, periallocortex and neocortex. The allocortex is composed of hippocampal and olfactory structures, which usually display three-layered organization. The periallocortex refers to agranular cortical structures located next to the allocortex. The neocortex includes so-called proisocortex, which mainly consists of parts of cingulate, parahippocampal and temporopolar cortices, and the typical neocortex (isocortex), which includes the remaining cortical regions.

During development, the developing cerebral cortex displays distinct transient lamination, which mainly includes subpial granular zone (SG), marginal zone (MZ), cortical plate (CP), subplate (SP) and intermediate (IZ), subventricular (SV) and ventricular zones (VZ) (Mai and Ashwell, 2004). As the cortex matures, the cortical plate will differentiate into mature cortical layers II-VI while the marginal zone will become mature layer I. The remaining transient zones will basically disappear and/or be replaced by white matter in the mature brain. For transcriptome analysis, the cortical samples from 4-12 post-conception weeks (pcw) include the whole wall (all layers) of the cortex while those from 13-38 pcw mainly include marginal zone, cortical plate and subplate. For all postnatal brains (0 months to adult) the cortical samples include layers I-VI and part of the underlying white matter. Finally, for some early time points, the primary motor and primary sensory cortices were sampled together, thus the term primary motor-sensory cortex (sample) was generated for these samples under neocortex. For the 15- and 21-pcw reference atlases, neocortical zones (SG, MZ, CP, SP, IZ, SV, and VZ) and cortical areas were defined mainly based on detailed analysis of *in situ* hybridization (ISH) data generated from the reference atlas specimens (Ding et al, 2011).

Gyral parcellation for the adult reference atlas was primarily based on an analysis of sulcal patterns, which serve as common correlative landmarks for the alternate gyral and cytoarchitectonic delineative views (Cortex – Gyral, Cortex – Mod. Brodmann). Cytoarchitectonic parcellation was derived from a combination of Brodmann (1909) and Von Economo (1929), as well as some modern neuroanatomical advances in human cortical mapping with modified Brodmann's nomenclature mostly used. Specifically, parcellation of the frontal and cingulate cortex: Petrides and Pandya (1999, 2002), Ongur and Price (2003) and Vogt *et al*. (2004). Parietal, temporal and occipital cortices (where Brodmann's nomenclature was not or less used): Caspers et al. (2013), Scheperjans et al. (2008), Ding et al. (2009), Ding and Van Hoesen (2010), Goebel et al. (2004). The ontology and delineation of hippocampus was derived from Rosene and Van Hoesen (1987), with slight modification according to Ding (2013).

Subcortical regions
For 15- and 21-pcw reference atlases, subcortical regions such as amygdala, basal nucleus, basal forebrain, thalamus, hypothalamus, cerebellum and brainstem were defined mainly based on detailed analysis of ISH and cytoarchitectural data. For the adult reference atlas, ontology and nomenclature for different subcortical regions are specified below.

Amygdaloid complex
The ontology for amygdaloid complex is mainly based on Johnston (1923) and de Olmos (2004) with reference to the nomenclature for non-human primates (Price et al., 1987). Specifically, the amygdaloid complex includes central, basolateral and corticomedial groups, as well as anterior amygdaloid area and intercalated nucleus of amygdala. Some of the amygdaloid transition areas and extended amygdaloid structures were separate from the amygdaloid complex.

Basal nuclei and basal forebrain
The ontology and nomenclature for basal nuclei and basal forebrain is commonly used and consistent with many resources. Briefly, the basal nuclei in this ontology include striatum and globus pallidus with the former consisting of caudate nucleus, putamen and nucleus accumbens. The basal forebrain contains septal nuclei, basal nucleus of Meynert, nucleus of diagonal band, islands of Calleja and nucleus subputaminalis of Ayala.

Thalamus
The ontology for thalamus is mostly based on Jones (2007) and Morel (2007). Thus, the thalamus includes epithalamus (habenular and paraventricular nuclei), dorsal thalamus, which consists of several nuclear groups, ventral thalamus (zona incerta and nucleus of the Forel field) and reticular nucleus of thalamus.

Hypothalamus
The ontology for hypothalamus mostly follows that of Saper (2004). The hypothalamus was thus divided into preoptic, supraoptic, tuberal and mammillary regions along the anterior-posterior axis. Each region, in turn, is basically divided into periventricular, medial and lateral zones along the medial-lateral axis.

Cerebellum and brainstem
The ontology for cerebellum is similar to that described by Schmahmann et al. (2000) and Naidich et al. (2008). The ontology and nomenclature for the brainstem, which is subdivided into midbrain, pons and medulla, basically follows the new version of the human brainstem by Paxinos et al. (2012).

REFERENCES

Brodmann K (1909) *Vergleichende Lokalisationslehre der Grosshirnrinde*. Leipzig: Barth.

Caspers S, Schleicher A, Bacha-Trams M, Palomero-Gallagher N, Amunts K, Zilles K (2013) Organization of the human inferior parietal lobule based on receptor architectonics. *Cereb Cortex*. 23:615-628.

De Olmus JS (2004) Amygdala. In: *The human nervous system, 2nd edition* (Paxinos G, Mai JK, eds.), San Diego, CA: Academic Press, pp. 739-868.

Ding SL (2013) Comparative anatomy of the prosubiculum, subiculum, presubiculum, postsubiculum and parasubiculum in human, monkey and rodent. *J Comp Neurol* doi: 10.1002/cne.23416.

Ding SL, Royall JJ, Facer B, Sweeney K, Dalley R, et al. (2011) High-resolution histological and molecular reference atlases of human fetal brain. Program: 857.06, 2011 Neuroscience Meeting Planner. Washington, DC: Society for Neuroscience. Online**.**

Ding SL, Van Hoesen GW (2010) Borders, extent, and topography of human perirhinal cortex as revealed using multiple modern neuroanatomical and pathological markers. *Hum Brain Mapp*. 31:1359-1379.

Ding SL, Van Hoesen GW, Cassell MD, Poremba A (2009) Parcellation of human temporal polar cortex: a combined analysis of multiple cytoarchitectonic, chemoarchitectonic, and pathological markers. *J Comp Neurol* 514:595-623.

Filimonoff IN (1947) A rational subdivision of the cerebral cortex. *Arch Neurol Psychiat* 58: 296-311.

Goebel R, Muckli L, Kim DS (2004) Visual system. In: *The human nervous system, 2nd edition* (Paxinos G, Mai JK, eds.), San Diego, CA: Academic Press, pp. 1280-1305.

Johnston JB (1923) Further contribution to the study of the evolution of the forebrain. *J Comp Neurol* 35:337-481.

Jones EG (2007) The thalamus. Cambridge, UK: Cambridge University Press.

Mai JK, Ashwell KWS (2004) Fetal development of the central nervous system. In: The human nervous system, 2nd edition (Paxinos G, Mai JK, eds.), San Diego, CA: Academic Press, pp. 49-94.

Morel A, (2007) Stereotactic atlas of the human thalamus and basal ganglia. New York, NY: Informa Healthcare.

Naidich TP, Duvernoy HM, Delman BN, Sorensen AG, Kollias SS, Haacke EM (2008) *Duvernoy's atlas of the human brain stem and cerebellum: High-field MRI, surface anatomy, internal structure, vascularization and 3 D sectional anatomy*. Vienna: Springer-Verlag.

Ongur D, Ferry AT, Price JL (2003) Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol* 460:425-449.

Paxinos G, Huang XF, Sengul G, Watson C (2012) *Organization of Human Brainstem Nuclei. In: The human nervous system, 3rd edition* (Mai JK, Paxinos G, eds.), San Diego, CA: Academic Press, pp. 260-327.

Petrides M, Pandya DN (1999) Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur J Neurosci* 11:1011-1136.

Petrides M, Pandya DN (2002) Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. *Eur J Neurosci* 16: 291-310.

Price JL, Russchen FT, Amaral DG (1987) The limbic region. II. Amygdaloid complex. In: *Handbook of chemical neuroanatomy, Vol. 5* (Bjorklund A, Hokfelt T, Swanson LW, eds.), Amsterdam: Elsevier, pp279-388.

Rosene DL, Van Hoesen GW (1987) The hippocampal formation of the primate brain: a review of some comparative aspects of cytoarchitecture and connections. In: *Cerebral cortex* (Jones EG, Peters A, eds.), New York: Plenum, pp 345–456.

Saper CB (2004) Hypothalamus. In: *The human nervous system, 2nd edition* (Paxinos G, Mai JK, eds.), San Diego, CA: Academic Press, pp. 514-550.

Scheperjans F, Eickhoff SB, Hömke L, Mohlberg H, Hermann K, Amunts K, Zilles K (2008) Probabilistic maps, morphometry, and variability of cytoarchitectonic areas in the human superior parietal cortex. *Cereb Cortex* 18:2141-2157.

Schmahmann JD, Doyon J, Toga AW, Petrides M, Evans AC (2000) *MRI atlas of the human cerebellum*. San Diego, CA: Academic Press.

Vogt BA, Hof PR, Vogt LJ (2004) Cingulate cortex. In: *The human nervous system, 2nd edition* (Paxinos G, Mai JK, eds.), San Diego, CA: Academic Press, pp. 916-949.

Von Economo C (1929) *The cytoarchitectonics of the human cerebral cortex*. London: Oxford.