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Review of Printed and Electronic Stereotactic Atlases of the Human Brain

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1. Introduction

The scientific developments of the latter half of the 19th century and the beginning of the 20th century supplied comprehensive data and insight on brain structure and function. Knowledge on structure and function provided strategies and tools for the management of previously lethal or highly incapacitating diseases, e.g. Parkinson's disease (PD) and tremor. A major challenge for neurosurgery was the endeavor to reach some deep and hitherto hidden regions inside the brain without damaging the surrounding tissue, since most of these small regions are vital and not directly visible *in situ*. Using the Cartesian coordinate system based on cranial landmarks, Victor Horsley and Robert Clarke introduced in 1908 a new apparatus that allowed them to accurately target subcortical nuclei of monkeys (Horsley & Clarke, 1908) with quasi-mathematical precision. A modified version of this device was adopted by Spiegel and Wycsis (1947) for human intracerebral interventions. Nevertheless, the space in which these mechanical devices were navigating still remained obscure and perilous. Almost four decades later, the parallel progress of neuroimaging shed light into the hitherto hidden structures and regions of the human brain. However, in order to find out appropriate pathways to specific functional units within clinically relevant targets the necessity of detailed brain maps was mandatory. Even with the great advance in neuroimaging in the last twenty to thirty years, it is still not possible to unequivocally delineate closely related subcortical structures by means of high-resolution computed tomography (CT) or in magnetic resonance image (MRI) (Coffey, 2009). For this reason, brain atlases derived from appropriate histological, histochemical, or immunohistochemical techniques on post-mortem human brain tissue continue to represent an important tool for functional neurosurgeons and brain researchers. To supplement the post-mortem anatomic maps, electrophysiologic in vivo recording of neuronal activity was added to neurosurgeries. This technique is intended to be an ancillary method to assist neurosurgeons in verifying their targets. In this chapter we will summarize and critically review the merits and the shortcomings of the most frequently consulted atlases. Some ideas on scope, form, and presentation of future atlases will be forwarded.

2. Printed stereotactic atlases

The history of human brain atlases begins in 1947, when the surgeons noticed that it was possible to adapt mechanical devices used in animals to navigate precisely the human brain. Therefore, it was mandatory to generate maps with coordinates of the uncertain territory in order to plan the best routes to avoid even minimal collateral damage and to focus the targets with high precision. Printed stereotactic atlases were considered to supply blueprints to neurosurgeons for intracerebral navigation.

2.1 Stereoencephalotomy (thalamotomy and related procedures), part I: methods and stereotaxic atlas of the human brain (Spiegel & Wycsis, 1952)
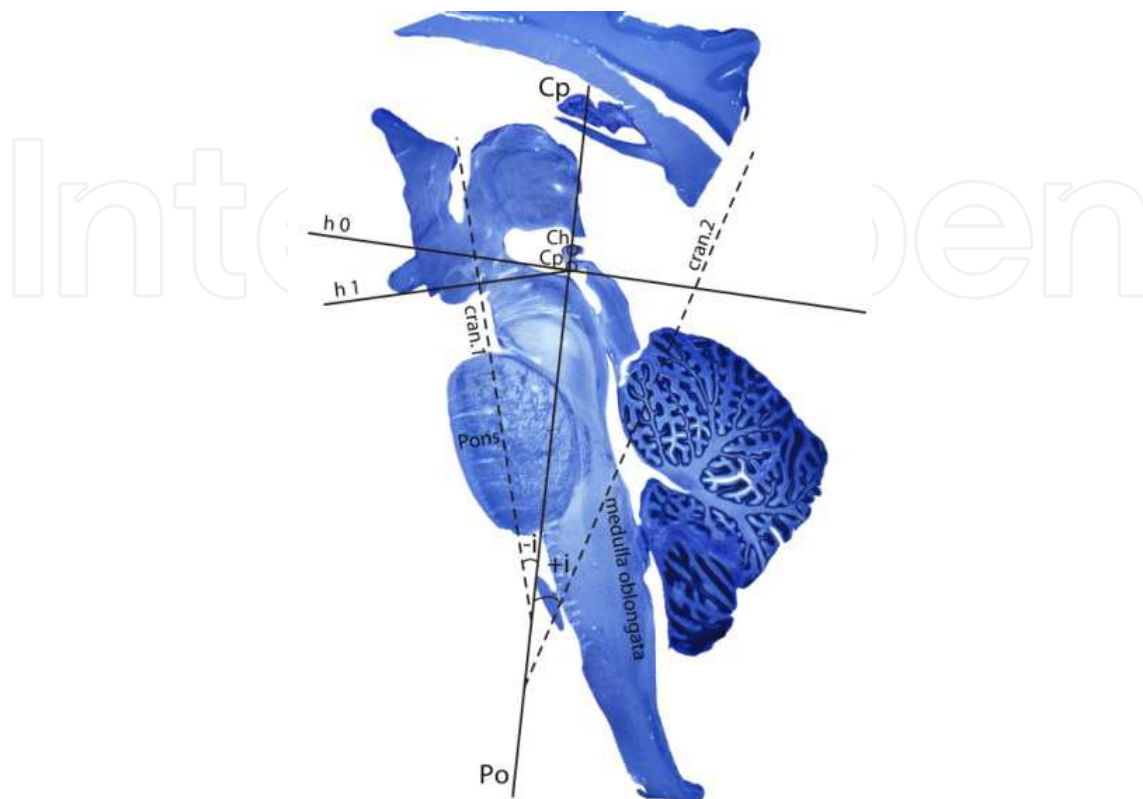
The first stereotactic human brain atlas was entitled *Stereoencephalotomy*. It was developed to solve the lack of accuracy of referenced systems based on cranial references and to allow the stereotaxic surgery to be performed in humans. It should be noted that since 1973 the term "stereotactic" is used for surgery in humans, whereas "stereotaxic" is used exclusively for neurosurgery in animals.

In 1947, Spiegel and Wycsis described the first human stereotactic instrument used routinely in subcortical surgery. It is based on the use of intraoperative radiographs, allowing the visualization of cerebral references. After the emergence of the technique of interventricular instillation of air (ventriculography), anatomical structures including the foramen of Monro (FM) and the calcification of the pineal gland could be used for localization of intracranial targets. With the advent of new contrast media it was possible to use new landmarks in the brain, such as the anterior commissure (AC), the posterior commissure (PC) and the intercommissural line (ICL).These new references are much more reliable than the former ones, as verified by Talairach (Talairach et al., 1957).With these new reference points at hand, the indication for neurosurgical interventions could be extended, since new targets appear within the coordinates of the stereotactic apparatus. Spiegel and Wycsis' (1952) atlas consisted of photographs of a series of coronal brain, sliced at regular intervals in relation to the posterior commissure and the midline, with a reference graph located at the edges of each section. Using this parameter, the surgeon was able to assess distances in millimeters in depth and laterality of subcortical targets with a known distance of the posterior commissure. Coordinates for many targets were derived from this concept, and neuroablative procedures became reality. These studies were the basic guidelines for targets used in pallidotomy for treatment of abnormal movements and mesencephalotomy for treatment of refractory chronic pain, published in 1950 by Spiegel and Wycis.

Prefrontal lobotomies were frequently performed in the days before the emergence of appropriate psychotropic medication. At the time of the development of stereotactic surgery, Spiegel hoped to refine this procedure to avoid the unwanted complications and deficits frequently associated with these procedures. With this in mind, the first use of the stereotactic apparatus was the coagulation of the dorsal median nucleus of the thalamus in patients with severe psychiatric disorders, seeking a less traumatic intervention than a lobotomy. Around the same time the use of stereotaxy for interruption of pain pathways, surgical treatment of abnormal movements, and drainage of fluid from pathological cavities, - , for instance, cystic tumors -, had also been proposed.

Initially, their reference coordinate system was the Cp-PO line (posterior commissure-pons line). This coordinate system was not simple and was not widely used. In their next work in 1962, Spiegel and Wycsis (Spiegel & Wycsis, 1962) assumed the intercommissural line as

standard reference system. The second part was a textbook and revised atlas updated from the first version. This atlas is currently out of print (Coffey, 2009).
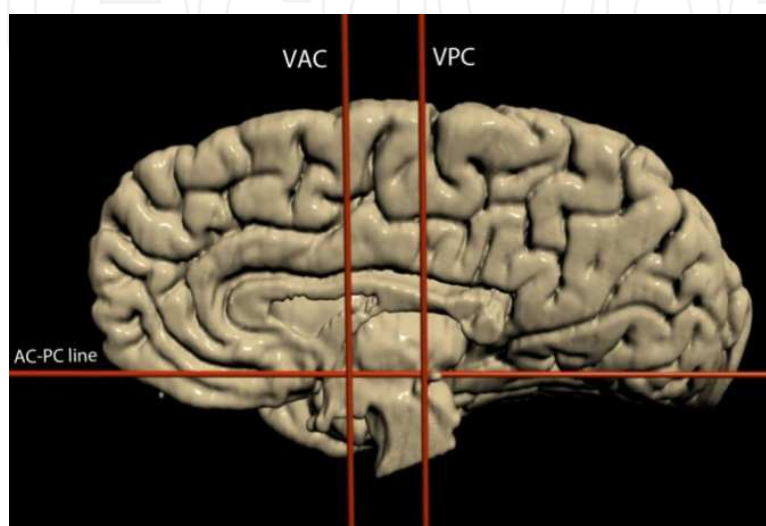

Main lines for spatial orientation are the mediosagittal Cp-Po line that connects the posterior commissure (Cp) with the bulbopontine sulcus. The h 0, a horizontal line (perpendicular to the Cp-Po-line) which crosses the Cp-Po-line at the level of the posterior commissure. The h1 line emerges in an acute angle at the crossing point of the Ch and the Cp and runs in a rostral direction. Cran.1 and cran.2 can be considered as ancillary lines. Cran.1 is perpendicular to h1 and forms an acute angle of 4° (-i) with the CP-PO-line, cran.2 like cran.1 leaves the Cp-Po-line with an inclination of 4°, however, posterior to the Cp-Po-line (+i).

Fig. 1. First intracerebral reference system proposed by Spiegel & Wycsis in 1952.

2.2 Atlas d'anatomie stéréotaxique: Repérage radiologique indirect des noyaux gris centraux des regions mésencéphalo-sous-optique et hypothalamique de l'homme (Talairach et al., 1957)

The most important contribution of this publication is the use of AC and PC as reliable intracerebral stereotactic markers and their stable relationship to deep brain structures. From this work, came the concept of Talairach's space. The Talairach's space is a coordinate system based on AC and PC as pivotal landmarks. Using the distance between them and the orthogonal plans erected, it is possible to compare the location of brain structures in two different brains, independent from individual differences. Because of the individual variations in the three dimensions of human brains, the distances measured in millimeters are applicable only to one individual. This becomes increasingly true with greater distance from the basal lines. Talairach concluded that dimensions given in millimeters can apply only in a general population to the gray central nuclei, whose dimensional variations remain moderate. For this reason they presented later the three-dimensional proportional grid system (Talairach & Tournoux, 1988).

Several brains were studied, but the atlas was based on a single specimen. Talairach used his double-grid stereotactic instrument to create perforations in the craniocerebral specimen filled with air in the ventricular system. It was mounted on a stereotactic apparatus and metal probes were introduced. Radiographs were taken in profile and the brain was then removed and sectioned. The paths of the probes in the brain were used to establish the directional planes. Accurate coordinate measurements and profiles were derived for deep cerebral nuclei, subnuclei, and tracts. The stereotactically marked brains were cut in either parasagittal or frontal sections along Talairach's standard planes.

The principal line for intracerebral orientation is the AC-PC line (also called the intercommissural line or ICL) that connects the superior edge of the anterior commissure with the inferior edge of the posterior commissure. Two perpendicular lines cut the AC-PC-line, the VAC, that runs through the center of the anterior commissure and the VPC, that runs through the center of the posterior commissure. Transformation of the ICL, VAC and VPC lines into planes yield the intercommissural plane (ICP), the anterior verticofrontal plane (VACp) and the posterior the verticofrontal plane, (VPCp) respectively.

Fig. 2. Talairach's stereotactic references.

The three-dimensional profiles of the thalamic nuclei and other structures were mapped on millimeter-ruled diagrams. The reference line was the intercommissural line. This line is widely used even to the present day. This atlas is currently out of print.

2.3 Introduction to stereotaxis with an atlas of the human brain (Schaltenbrand & Bailey, 1959)

Schaltenbrand and Bailey published the most comprehensive and detailed stereotactic atlas. They studied 111 brains that were sectioned in the coronal, sagittal, and horizontal planes. Variability diagrams were based on seven specimens. Hassler and Wahren completed profound studies of nuclear structures in coronal and parasagittal sections. Akert, Bucy, Walker, Snider, and Hassler contributed with detailed chapters on the physiology and pathophysiology of deep structures of the human brain. Nearly forty years later, this atlas also contributes immensely to functional neurosurgeons, and it could be the most used atlas in the pre-CT era. Even today, the expanded 1977 edition with the most useful features of this work is used world-wide. Their coordinate system appears to be derived from Talairach's space, but shows slight differences.

2.4 A stereotaxic atlas of the human thalamus and adjacent structures: A variability study (Andrew et al.,1969)

Since the beginning of stereotactic surgery, the main concern of the neurosurgeons was precision. The authors noted that all the previously presented atlases were based on very few specimens and even in the Schaltenbrand's atlas, despite the high total number of brains, only 7 out 111 were comprehensively studied. It was concluded that the stereotactic coordinates of subcortical nuclei were inadequately established, and that the variations would be so great that the procedures could not be reliably done with these coordinates.

The authors thus presented a variability study, aiming to compensate for this lack of precision. They studied nineteen brains, and focused on thalamic nuclei variability. Besides the thalamus, the atlas includes adjacent basal ganglia, and medial temporal lobe structures. It consists of statistical analysis of the data, with probability tables and distances to important ventricular reference points such as the foramen of Monro (FM), PC and midcommisural plane. It was surely an important work to define variability patterns in pre-CT/MRI era.

They used the FM-PC line and the total thalamic length (TthL) as reference system instead of the Talairach's space, although they have measured the AC-PC distance as well.

2.5 Variations and connections of the human thalamus (Van Buren & Borke,1972)

These authors, together with Schaltenbrand and Talairach, published one of the most important atlases of that time. The atlas is the result of a meticulous work on this challenging structure of the human brain, and it comprises a detailed cytoarchitectonic description of the individual thalamic nuclei. The literature on the connections of each nucleus is also reviewed. A special section of the book is dedicated to present the primary lesions (intervention) and secondary thalamic degeneration in fifty-four patients due to stereotactic procedures. The authors care about questions such as correcting differential shrinkage with computational tools, and variation of the position of thalamic nuclei in relation to midline, anterior, and posterior commissures.

2.6 The human somesthetic thalamus with maps for physiological target localization during stereotactic neurosurgery (Emmers & Tasker, 1975)

In this work Tasker and Emmers have presented a detailed map for electrical stimulation of the thalamus, with 2mm interval stimulation. During stereotactic procedures performed with awake patients, the distribution of somesthetic responses elicited by electrical stimuli was projected into the templates and used to build a three-dimensional homunculus of the somesthetic thalamus. Tasker emphasized that physiologically defined anatomy rather than blind obedience to atlas coordinates should determine how to conduct functional stereotactic operations.

2.7 Atlas for stereotaxy of the human brain with accompanying guide (Schaltenbrand & Wahren,1977)

According to the preface of the second edition of their atlas the first one was "an exploration of a new field of clinical anatomy." The latest edition concentrates on clinically relevant issues. The authors emphasized the importance of the myelin sections and reduced the

number of macroscopical sections that proved to be of less interest. Thus the material could be condensed into a single and more practical volume. Some of the modifications took into account promising procedures at that time, such as operations on the small nuclei of the hypothalamus to treat deviant sexual behavior and vegetative disorders. They also added electroanatomical observations on the localization of important trigger points and radioanatomical observations in more than 300 patients.

The 111 brains, ranging in age from neonate to 86 years used in the preparation of this atlas were collected at the University of Würzburg, University of Lund (Germany) and the Sodersjuhuset in Stockholm (Sweden). They have considered to use Reid's plane (the plane that extends from the lower margin of the orbit to the center of the external acustic foramen) as reference, however the examination of the macroscopic series did not reveal consistent spatial relations between points on the outer surface of the skull and the subcortical structures, and they chose the AC-PC axis and the perpendicular line erected on the middle point of the two commissures as the basis for their system of reference.

The extremely careful work with great histological sections through the most clinically relevant structures inserted in a consensual reference system made this atlas one of the most consulted until the present day. This atlas is still in print, due to its practical value and use in functional neurosurgical procedures. Many other authors used this work to construct a computational tool for stereotactic surgery.

2.8 Stereotaxic atlas of the human brainstem and cerebellar nuclei: A variability study (Afshar et al., 1978)
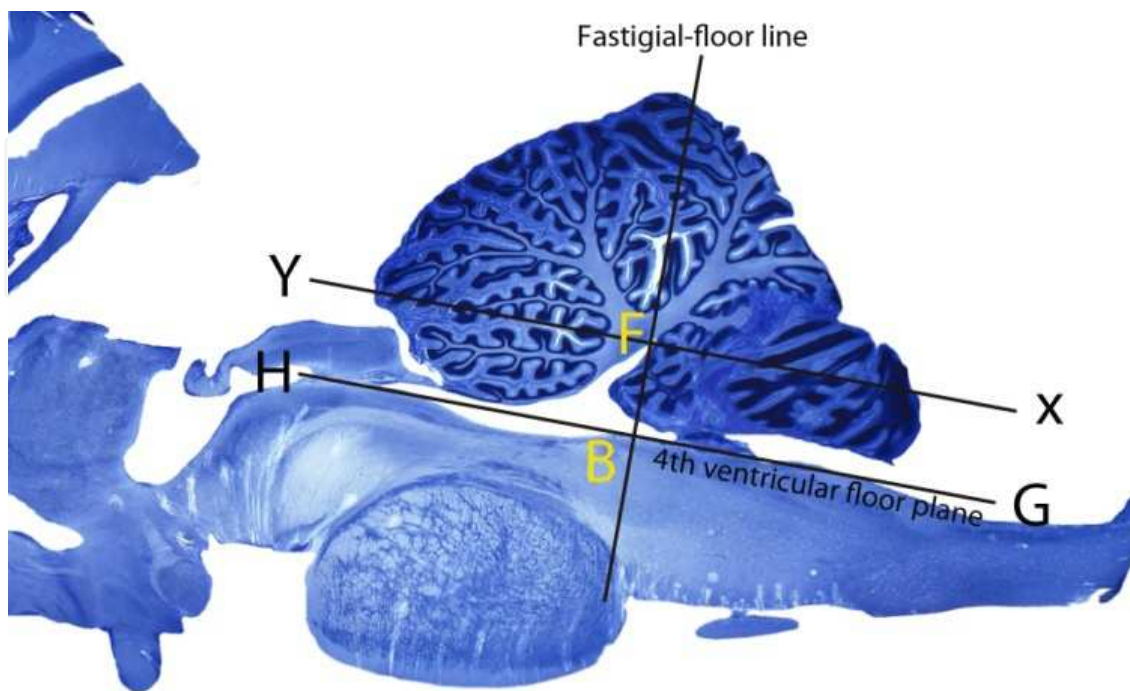
In the early '70s, strategies for the treatment of spasticity due to cerebral palsy and other disturbances of muscle tone and posture by ablation of the dentate nucleus of the cerebellum were developed. In this context, Afshar focused on the cerebellar nuclei and brainstem structures involved in muscle tone disturbances and pain.

Thirty brains were studied using positive-contrast ventriculography and stereotactic marking of the specimens *in situ*. Their atlas comprises a variability and probabilistic study comparable to their previous study in 1969. They present a coordinate system based on the fastigium-floor line (FFL), and orthogonal to the ventricular-floor plane.

2.9 Co-planar stereotaxic atlas of the human brain: Three-dimensional proportional system: An approach to cerebral imaging (Talairach & Tournoux, 1988)

This work can be considered one of the most important in the field of brain mapping. Its focus is less on histology and architectonic and more on presenting the concept of proportionality and a new coordinate system, the so called Talairach space.

The Talairach's proportional grid system is based on the three dimensions (length, height, and width) of the human brain. The reference planes are defined as: the midline, defining the sagittal plane; the intercommissural plane that is obtained from the line that passes through the superior edge of the AC and inferior edge of PC, defining the horizontal plane; and two verticofrontal planes that intersect the anterior and posterior commissures (named VACp and VPCp). The authors state that direct distance coordinates vary widely from one brain to another and the variation is greater considering points far from the midline.

The reference lines of Afshar et al. are confined to brainstem and cerebellar structures. The ventral HBG line runs in a rostro-caudal direction tangentially to the floor of the IVth ventricle. The parallel dorsal YFX line passes the tip of the fastigium. A line perpendicular to YX and HG goes likewise through the tip of the fastigium. Its intersection with YX defines F ; the one with HG defines B.

Fig. 3. Coordinate system proposed by Afshar et. al., 1978.

However this variation is proportional for each brain, and they propose to divide the brain in proportional voxels or "orthogonal parallelograms."
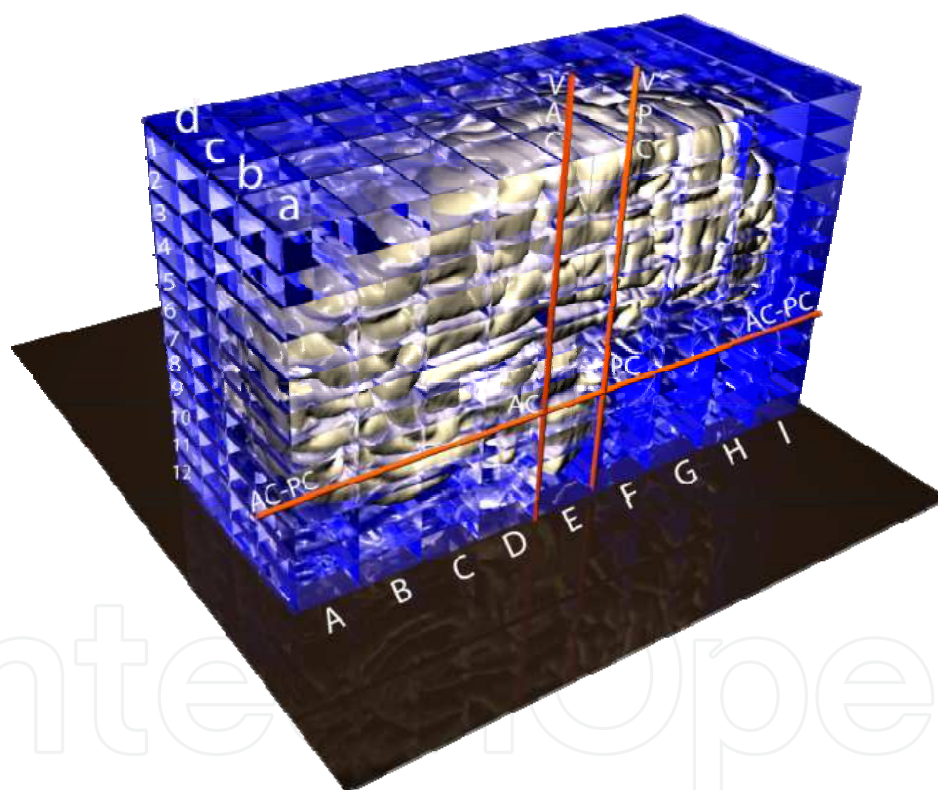
Each hemisphere is divided in twelve parts (1-12) in its supero-inferior (z) axis, in nine parts (A-I) in its anteroposterior (y) axis and in four parts (a-d) in the laterolateral (x) axis. Each voxel has the following dimensions: x: one-fourth of the distance between midline and the most lateral point of the parietotemporal cortex, named a-d ; y: The voxels located anterior to AC have ¼ from the distance from AC to the frontal pole(named A-D). The voxels located posterior to PC have ¼ of the distance from PC to the occipital pole (named F-I), and finally the AC/PC distance is the 9th voxel (named E) and can be divided in thirds, called "mini-voxels"; z: the voxels located above the IC line have 1/8 of the distance between IC line and the highest point of the parietal cortex (called 1-8) and the voxels located below the IC line have ¼ of the distance between the IC line and the most inferior point of the temporal cortex (named 9-12). This voxels are fixed for every brain, allowing the normalization between two different subjects having in mind these proportions and not absolute distances in millimeters. The proportional grid system is the greatest contribution given by this work.It allows us to warp our atlases to the patient's MRI using this proportionality. The term "warping" is used in neuroimaging to describe the process of distorting an image (e.g.,

atlases) to fit other similar images (e.g. MRI). When two brains are normalized using this proportional system a " Talairach transformation" is performed.

Even with some known disadvantages, such as inter-slice distances variable between 2 and 5 mm, inconsistencies of orthogonal planes and assuming left/right symmetry, this atlas is widely used by neurosurgeons while planning interventions.

2.10 Multiarchitectonic and stereotactic atlas of the human thalamus (Morel et al., 1997)

Morel's et al. (1997) atlas is based on standard as well as histochemical and immuniohistochemical methods. Advanced neurochemical markers were used to further characterize thalamic nuclei and delimit subterritories of functional significance for stereotactic explorations. The objective was to improve the anatomical definition and precision of thalamic targets.

The principal Talairach planes (ICp, VACp, VPCp) can be further parcelated by nine coronal planes (A-I), by four sagittal planes (a-d), and by twelve horizontal planes (1-12). Independent of individual hemispheric sizes, each hemisphere will consist of a total of 9x12x4 = 432 voxels. The coronal plane E, based on the AC-PC distance, represents a kind of core structure. Its dimensions are directly measured from the MRIs. The relative voxel sizes of A to D, F to I, a-d and 1-12 are a matter of convenience. They are derived from the maximal lobar extensions rostral, caudal, and lateral from VAC and VPC, and ventral from the AC-PC plane. They are expressed as fractions of the respective plane (1/4 in the coronal plane rostral and caudal to E, ¼ in the sagittal plane corresponding to a – d, 1/8 in horizontal planes dorsal to the AC-PC plane, and ¼ in horizontal planes ventral to the AC-PC plane).

Fig. 4. Hemisphere inserted in Talairach's space

They could observe the distribution of immunostaining among the thalamic groups and correlate specific markers to functional units.

One interesting technical aspect of this atlas is the correction for shrinkage factors. It was done by means of preoperative MRI from two patients who underwent medial thalamotomy for cancer-related neurogenic pain and who died later from their disease. Intercommissural distances were measured post-mortem at the end of histological processing, and an additional distortion factor was taken into account for coordinates between sections, by measuring the distance between two coronal sections intersecting the centers of the two commissures. The most valuable contribution of this atlas is though the presentation of a chemoarchitectonic organization of the human thalamus.

2.11 Atlas of the human brain (Mai et al.,1998, 2003)

This atlas consists of printed sections and digital media, making it especially easy to use. The first section is a topographic and topometric atlas, in which *in vivo* and *in vitro* MRI scans are compared to whole head sections in horizontal, coronal and sagittal plans. The myeloarchitectonic atlas is based on serial coronal sections through a single hemisphere from a 24-year-old male. Although the templates give detailed information about cytoarchitectonic fields, it is hard to imagine how they could have been segmented from the sections presented on the book, since the staining allows very good contrast between gray and white matter; however, it is hard to define cytoarchitectonic borders with this method. It is a comprehensive study, and its most interesting features are the *in vivo* and *in vitro* MRI comparison to the cadaveric slices, and the user-friendly interface in the digital version.

2.12 Stereotactic atlas of the human thalamus and basal ganglia (Morel, 2007)

In 2007, Morel presented this atlas with the main objective to combine high anatomical resolution (taking advantage of new staining methods) and stereotactic precision. This paper presents a collection of diagrams of the human thalamus, basal ganglia, and adjoining structures, consisting of a series of maps in the three stereotactic planes, and comparisons between brains with similar and differing intercommissural distances. This work, like the previously presented one ten years before, examines the distribution of different neurochemical markers in the thalamus and basal ganglia for comparison with non-human primate data.

Fiber tracts leading to the thalamus are also described, and there is a correlation between histological maps with MRI images. They compare also the individual representations, giving an idea of variability.

This atlas is especially useful in functional neurosurgery for research purposes to those who want to understand the connections and plan new targets for neurosurgical interventions in diseases involving the thalamus and basal ganglia.

2.13 Summary of materials and methods used in the preceding publications

To give a better overview of various details, ranging from the number of cases studied to the reference coordinate systems, a table will summarize the salient features concerning materials and methods applied.

Reference	Nr. of brains and sections	Staining and other investigative tissue methods	Orientation of sections and interval	Range of Slices	Coordinate System	MRI
Spiegel & Wycsis,1952	1 brain (30 sections)	Unstained (1) and myelin-stained (2)	(1)cor.,sag., horiz.and oblique through brainstem (5mm int.) (2)cor. (2-4 mm) and oblique through brainstem (5mm)		PC-PO line MSP	No
Talairach et al., 1957	1 brain	Unstained and Myelin-stained			ICP, MSP, VACp , VPCp	No
Schaltenbrand & Bailey,1959	111 brains (7 brains for variability study)	Unstained (1) and myelin – stained (2)	(1)16 coronal (1- 4 mm) and 18 sagittal (0.5 to 2.5 mm);(2)20 horizontal	16.5 mm ant. to AC and 16.5 mm post.to PC;2.0 - 27.5mm lat. to midline;16mm above to 9.5mm below midcom. pt.	ICP MSP McomP	No
Andrew et al., 1969	19 brains	Nissl and myelin stained from 1 brain	21 coronal (1 mm) and 17 sagittal (1mm)	1-21 mm behind FM;3-20 mm from midline; includes thalamus, basal ganglia, and medial temporal lobes.	FM-PC line TthL	No
Van Buren &Borke, 1972	6 brains individual profiles and 25 hemisph. for gross anatomy variability	Cresyl-violet, myelin and Golgi preparations	10 sagittal (0.5 to 4mm); 8 horizontal (3.5mm) ; 10 coronal sections	2-25mm lat.to midline parallel to ICP; 17mm above to 8.1 mm below IC; 23.4 mm ant. PC - 47mm post. PC	ICP MSP VAC	No
Emmers& Tasker, 1975	2 brains: 1 for macrose-ries 1 for microseries	Electrical stimulation at 2mm intervals and mapping of the somesthetic responses elicited in awake patients; results projected into the templates	5 sag. and 5 cor. plates; 10 sag. and cor. whole brain sections	Cut at 9, 11,13.5,16 and 18 mm lat. to midline; 8.5, 10 , 11, 12.5 mm post. to the midcom. point	ICP MSP VAC	No

Reference	Nr. of brains and sections	Staining and other investigative tissue methods	Orientation of sections and interval	Range of Slices	Coordinate System	MRI
Schaltenbrand &Wahren, 1977	34 sec. for macro and 57 sec.for microseries (frozen sec. 30μm) Paraffin used to brainstem and cerebellum	Unstained(1), myelin-stained and Nissl (2)	(1)19 cor.,5 sag., 6 horiz.from 1 brain, and 4 from another; (2) 20 cor., 17 sag.and20 horiz.	(1)57 mm ant. - 44 mm post. to AC; 0 - 22mm from midline; 18 above-20mm below ICL; 5-28mm below ICL; (2)16.5 mm ant.-16.5mm post midcom. line 1.5-27.5 mm lat. Midline 16.0mm above to 9.5mm below ICL	ICP MSP McomP	No
Afshar et al.,1978	30 brains	Myelin-stained	(1)54 plates, 1mm thick ;(2) 12 cerebellar plates	(1)23mm rostral to 30mm caudal to FFL; 1mm rostral to 10mm caudal to FFL	VFP FFL Fastigial point	No
Talairach& Tournoux,1988	1 brain cut sagittaly, frontal and horizontal sections were interpola-ted	Anatomic sections, that are drawn as a result of tracing the sections	36 sagittal (1-4mm int.); 38 frontal (5mm int); 27 horizontal (5mm int)	Right: 18 sec 0-62mm ;Left:18 sec 0-61mm ;0-65mm ant. To VAC; 0-100mm post VAC;0-6.5 mm above ICL;0-4.1mmbelow ICL	ICP MSP VAC	Yes
Morel et al.,1997	9 thalamic frozen blocks cut in 40μm thick slices from 5 brains	Nissl, myelin and Immunohystoc hemestry parvalbumin (PV), calbindinD-28K (CB), and calretinin (CR)	3 blocks sagittal, 4 horizontal and 2 coronal	Region of interest: thalamus	ICP MSP VAC	Preopera tive MRI of 2 patients
Mai et al.,1998,2003	6 brains – macrose-ries (frozen, 1 cm thick) and 1 hemisphere for Microseries (paraffin)	(1)Sudan red or Sudan Black B (2)Hematoxyli n- or sudan black B for myelinated fibers	17 horizontal;15 coronal and 8 sagittal; (2) 69 coronal sections	(2) 60mm ant.AC-100 mm post. AC (100μm)	ICP MSP VAC	Yes for the macroser ies

Reference	Nr. of brains and sections	Staining and other investigative tissue methods	Orientation of sections and interval	Range of Slices	Coordinate System	MRI
Morel, 2007	7 brains, frozen, cut 40-50µm thick	Nissl and cresyl violet, myelin;parvalbumin (PV), calbindinD-28K (CB), and calretinin (CR) ;antibodies anti tyrosine hydroxylase (TH), Acetylcholinesterase (AChE) or immunore-acted with SMI-32	Thalamus : 26 horizontal,24 sagittal Basal ganglia: 25 sagittal and coronal	14 mm superior to 8.1 mm inferior to ICL;4.6 to 25.8 mm from midline; 3 to 41.5 mm anterior to PC; 3 to 27mm lateral to midline	ICP MSP VAC	Yes, from 2 brains, obtained 10 days and 1 year after fixation in formalin

Definitions: PC-PO line: connects the center of posterior commissure (PC) to the ponto-medullary sulcus (posterior border of the pons) and the midsagittal plane (MSP); ICL- intercommissural line: line that passes through the superior edge of the anterior commissure (AC) and inferior edge of PC; ICP- intercommissural plane: plane obtained from the ICL, defines the horizontal plane; MSP-Midsagittal plane: obtained from midline; VACp:Verticofrontal plane is formed by VAC line, that is a vertical line traversing the posterior margin of the AC: VPCp is the verticofrontal plane perpendicular ICL crossing it at PC; MComP: Midcommissural plane is erected from the midcommissural point, that is the midpoint of the ICL;The FM-PC line is the distance between the posterior inferior margin of the foramen of Monro (FM) to the midpoint of the ventricular surface of PC;The total thalamic length (TthL) is the distance between the FM and the top of the pulvinar;The ventricular-floor plane (VFP) is the plane defined by the floor of the fourth ventricle. Perpendicular to this plane and reaching the fastigium (apex of the roof of the fourth ventricle) is the fastigium-floor line(FFL).

Table 1. Printed stereotactic atlases based on number of cases studied, histological protocols, planes of section, coordinate systems, and reference to neuroimaging.

3. Three-dimensional electronic atlases based on printed two-dimensional stereotactic atlases

Printed stereotactic atlases have an intrinsic limitation due to the fact that they consist of a two-dimensional representation of the brain, which is a three-dimensional structure (Yelnik et al., 2009).The first solution encountered in literature to overcome this problem was simply to scan the previously published 2D templates into a computer and delineate 3D volumes on them. This was the beginning of the development of deformation algorithms and volumetric visualization of anatomical structures that would change the standard on neurosurgical planning.

3.1 Creation of a three-dimensional atlas by interpolation from Schaltenbrand-Bailey's atlas (Yoshida, 1987)

In 1987 Yoshida proposed the creation of a 3D atlas of the human brain based on the interpolation of the 2D templates of the Schaltenbrand-Bailey's atlas. Although the rendering resulted in great three-dimensional incoherency due to the lack of correction of the linear and non-linear tissue distortions present at the original sections, this atlas is important as the first of its kind and of the concept of referring to a volume instead of confining exclusively on two-dimensional representations of the neural tissue.

3.2 Multiple brain atlas database and atlas-based neuroimaging system (Nowinski et al., 1997)

Nowinski and his collaborators started in 1997 a project in which four previously published atlases were digitized, enhanced, segmented (color coded or contoured), labeled, aligned, and organized into volumes for the purpose of developing an atlas-based neuroimaging system for analysis, quantification, and real-time manipulation of cerebral structures in two and three dimensions. A software was developed that is available in a CD-ROM called "Electronic Clinical Brain Atlas-ECBA." It is impressive in terms of three-dimensional visualization of the structures; however, due to some inaccuracies inherent in the original print atlases, three dimensional structures reconstructed from Schaltenbrand & Wahren atlas are often convoluted and displayed in unrealistic shapes. As noticed and discussed by the authors in this paper, a given point in the stereotactic space may have up to three different labels on the Talairach & Tournox atlas, due to inconsistent orthogonal plates. Nevertheless, important questions about the 3D accuracy of the most-used atlases were evidenced.

3.3 Automated atlas integration and interactive three-dimensional visualization tools for planning and guidance in functional neurosurgery (St-Jean et al., 1998)

The authors created a deformable volumetric atlas of the basal ganglia and thalamus from the Schaltenbrand and Wahren atlas (SW atlas) to help neurosurgeons navigate through MRI-invisible structures. They developed also a visualization platform that permits manipulation of the merged atlas and MRI data set in two- and three-dimensional views. A really interesting and new method of correction of errors was developed by this group. After digitizing the sections and the transparent overlays from the SW atlas, they aligned and segmented the nuclear contours based on the overlays and performed an interpolation to create a 3D volume. The alignment was based on the original grid, and they noted that the grid structure present in the atlas was placed on the cryotome images subsequent to photography, and so even precise alignment with respect to the grid is no guarantee that the underlying slices were not themselves distorted during the slicing process. However, they developed a methodology for matching automatically the slices with the 3D model. The atlas is registered point-to-point (250 homologous landmarks identified by a neuroanatomist) to a model MRI or standard reference volume. Even though any MRI could be chosen, they opted by the Colin27 that is the result of an average of 27 MRI scans of the same subject. As they have a labeled MRI based on the SW atlas, an algorithm called ANIMAL (Automated Nonlinear Image Matching and Anatomical Labeling) computes a nonlinear transformation to register the patient's MRI with the pre-labeled

Colin27.The most important contribution from this work was the use of a special algorithm to align and segment the images and the use as reference a MRI standard volume, the Colin27.

References	Original Atlas	Method	Correction of distortions of the original atlas and segmentation	Registration and atlas-to-patient normalization
Yoshida, 1987	Schaltenbrand& Bailey,1959	A 0.5-mm step atlas was interpolated from the original atlas		
Nowinski et al.,1997	Talairach& Tournoux,1988, 1993; Schaltenbrand& Wahren,1977; Ono et al.,1990	The print atlases listed were digitized, enhanced, segmented , labeled, aligned, and organized into volumes	Manual correction of rotation and overlay-plate misregistrations. Some of the sources of errors cannot not be corrected	Registration based on max.dimensions of the brain and head of caudate, optic tract or putamen used as landmarks.Talairach's Transformation is applied
St-Jean et al.,1998	Schaltenbrand& Wahren,1977	Digit.sec. and transp. overlay, aligned and extracted 2D surfaces based on it and interpolated sec.	Slice-to-slice spatial inconsistencies in structure contours were considered to be small, and thus not accounted for. ANIMAL algorithm warps atlas to Colin27	ANIMAL algorithm warps the pre-labeled Colin27 to patient's MRI
Nowinski and Belov, 2003	Talairach& Tournoux, 1988	Digitized and processed the original print plates	Added structures to original templates to improve 3D consistency; developed algorithms to reformat the atlas to ICP	Talairach landmarks are set and then Talairach's Transformation is applied
Ganser et al, 2004	Talairach& Tournoux, 1988	Digitized and used only the 38 coronal plates	Interpolated additional cross-sections and applied algorithms to enhance the 3D coherence	Correspondences between the atlas and the patient are established in an automatic fashion nonrigid approach;

At variance with Table 2 data and 3D reconstructions were generated by the authors from new series of brains and details on histological procedures and data manipulation are listed.

Table 2. Electronic atlases derived from previously printed 2D stereotactic atlases Authors, sources, digital manipulation, and registration are listed.

3.4 The cerefy neuroradiology atlas: A talairach–tournoux atlas-based tool for analysis of neuroimages available over the internet (Nowinski & Belov, 2003)

The article published in 2003 introduces an atlas-assisted method and a tool called the Cerefy Neuroradiology Atlas (CNA), available over the internet for neuroradiology and human brain mapping. The Talairach & Tounoux atlas is presented in digital format and can be warped to the patient's MRI scan by means of a Talairach transformation. The Talairach landmarks (AC, PC, the most lateral point of the parietotemporal cortex, the most anterior point of the frontal cortex, the most posterior point of the occipital cortex, the most superior point of the parietal cortex, and the most inferior point of the temporal cortex) are set manually or semi-automatically and a linear transformation is performed. The great achievements of this atlas are the ease of use, new atlas-user interface, and availability over the internet.

3.5 A deformable digital brain atlas system according to talairach and tournoux (Ganser et al., 2004)

The authors have developed a digital version of the Talairach &Tournoux atlas. The main goal is to assist neurosurgical planning rather than brain mapping. They present a 3D representation of most of the brain structures contained in the Talairach atlas. They have also developed a tool which has a non-rigid matching capability, allowing the standard atlas structure to be warped to an individual brain MRI, even when lesions such as tumors are present. The great contribution of this work is the development of the nonlinear algorithm used to warp the atlas to the patient's MRI, despite the need for substantial nonlinear transformations.

4. Three-dimensional electronic atlases based on histological data

The digitization of previous published atlas led to problems in accuracy due to errors inherent in the technique used to construct them. In order to achieve better precision and accuracy in the 3D atlases, three groups have proposed to generate their electronic three-dimensional reconstructions based on own histological sections instead of aligning and trying to correct previous published templates.

4.1 The creation of a brain atlas for image guided neurosurgery using serial histological data (Chakravarty et al, 2006)

Until 2006, the group from MNI (Montreal Neurological Institute, Canada) used the atlas developed by St-Jean et al., 1998 to program neurosurgical interventions. However, some shortcomings were recognized, including limited inherent resolution in the slice direction, limited number of structures, and some small mis-registrations between the digital atlas and the Colin27 MRI average that are propagated to patient MRI data during the atlas customization procedure. In this manuscript, the authors addressed these limitations and presented a technique for the creation of a brain atlas of the basal ganglia and thalamus derived from serial histological data. The technique used was identical to the one used in St-Jean's (1998) atlas. However, in the latter instance own histological preparations were available instead of scanned figures from the Schaltenbrand & Wahren atlas. The authors digitized coronal histological sections and delineated 105 anatomical structures in them. A slice-to-slice nonlinear registration technique to correct for spatial distortions was

introduced into the histological data set at the time of acquisition. Since the histological data were acquired without any anatomical reference, this registration technique was optimized to use an error metric which calculates a nonlinear transformation minimizing the mean distance between the segmented contours between adjacent pairs of slices in the data set. To register the atlas to Colin27, a pseudo-MRI was created by setting the intensity of each anatomical region defined in the geometric atlas to match the intensity of the corresponding region of the reference MRI volume. This allowed the estimation of a 3D nonlinear transformation using a correlation-based registration scheme to fit the atlas to the reference MRI. The result of this procedure was a contiguous 3D histological volume, a set of 3D objects defining the basal ganglia and thalamus, both of which are registered to a standard MRI data set, to be used for neurosurgical planning.

4.2 A three-dimensional, histological and deformable atlas of the human basal ganglia. I. Atlas construction based on immunohistochemical and MRI data (Yelnik et al., 2007)

The French group describes in detail the construction of an atlas of the human basal ganglia. One brain was selected for reconstruction, and prior to the removal from the skull it was subject to MRI acquisition and then cryosectioned. The MRI was used for the coregistration of the atlas and permitted the production of more consistent 3D surfaces. Three different software tools were used in this study. A Threedimensional Tracing Software application (TTS) was developed for the purpose of digitization and processing of serial cerebral contours. The second tool is called Yav++ and its principal features include comparison and fusion of 3D images in multiplanar viewers as well as a 3D camera allowing visualization of serial contours, 3D surfaces, and 3D images in the same image. The last software tool is called BALADIN software, and it is an automatic image registration algorithm that allows registration of 2D or 3D images through an intensity-based block-matching approach. The novelty of this atlas is the MRI acquisition, which represents the core data element of the study.

4.3 A mean three-dimensional atlas of the human thalamus: Generation from multiple histological data (Krauth et al., 2010)

The stereotactic anatomical atlas under consideration consists of a three-dimensional thalamic model derived of a mean from six series of histologically processed brain sections. Postmortem MRIs are available for three of the stacks. The authors recommend that atlases should be based on a population instead of individuals. Therefore, previously studied stacks (Morel, 2007) were reconstructed based on multiarchitectonic criteria and integrated by an iterative algorithm -the so called bootstrap approach- to result in a three-dimensional average from three brains. The authors contend that their atlas improves the previous work on thalamic model reconstruction in several aspects. Firstly, while those models are based on the geometry seen in a single stack, their model incorporates topological and geometric details from different stacks and different stereotactic directions. Secondly, it would represent the average anatomy of several specimens instead of a single one, which would remove the bias towards a specific individual. This paper describes mainly how previous stacks can be used to build an average model of the human thalamus and the advantages of this kind of approach.
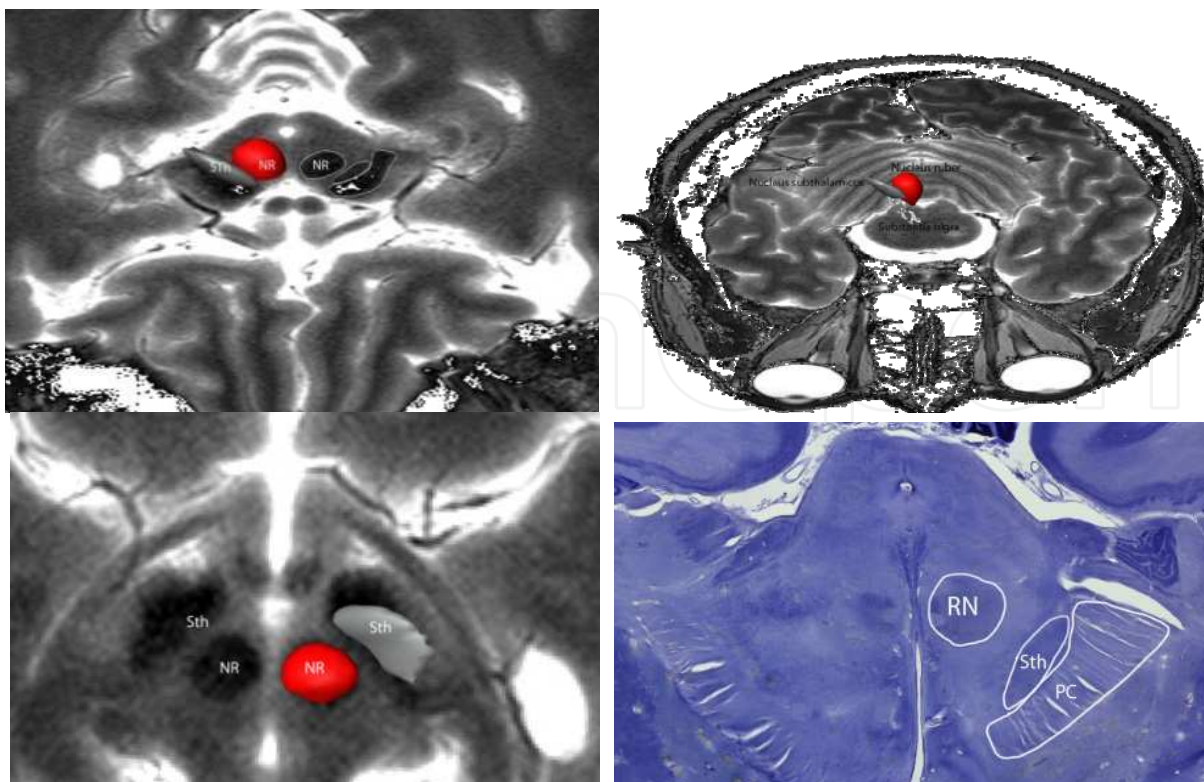
Reference	Nr of brains and Sections	Methods	Staining and other methods	Orientation and interval of sections	Range of Slices	Coordinate System	Correction of tissue deformation	Registration and atlas-to-patient normalization
Chakrava-rty et al., 2006	1 block from the left hemisphere (86 pairs of slices)	Mounted on paraffin; 105 anatomical structures manually delineated	Luxol Blue (myelin) Nissl(cell Bodies)	Coronal sections (0.70 mm interval)	Thalamus, hypothalamus, basal ganglia amygdala and hippocampus	ICP MSP VAC	The ANIMAL slice-to-slice registration procedure is applied	2 Steps ANIMAL application
Yelnik et al, 2007	1 Brain 800 sections	Frozen sections, 70µm thick; Post mortem MRI	80 sections Nissl-stained ; 80 sections immunostaining for calbindin	coronal sections	Basal ganglia	ICP MSP	Automated Process-ing for data coregistration and semi-automatic processing	BALADIN algorithm
Krauth et al.,2010	3 Brains (6 stacks), frozen, cut at 40-50 µm	Postmortem MRI (3 stacks);algorithm "bootstrap approach" was used to construct an 3D average	Nissl ; Myelin; Calcium-binding proteins(non-phosphorylated neurofilament protein and Acetylcholine sterase	(0.9 or 1.0 mm) intervals	Thalamus, basal ganglia, subthalamic fiber tracts	ICP MSP VPC	Calculated distortion factors from ICL mesurement	Not described

Table 3. Three-dimensional electronic atlases based on histological data

4.4 The São Paulo-Würzburg electronic atlas of the human brain initiative

Since 2005, the Brain Bank of the Brazilian Aging Brain Research Group (BBBABSG) of the University of São Paulo Medical School (USPMS) collaborates with researchers interested in neuroimaging-neuropathological correlation studies including dementias, white matter hyperintensities, and epilepsy. As a particularity, the BBBABSG is linked to the MRI section of the USPMS, so the brains can be scanned postmortem in-situ within a short postmortem interval.

At the Julius-Maximilian University of Würzburg (Germany), a fast, reliable, and easy to use celloidin method for serial sections of the human brain has been developed (Heinsen et al., 2000).

Cytoarchitectonic 3D contours of red nucleus (NR or RN, in red), subthalamic nucleus (STh in gray), and substantia nigra (in white) merged to the MRI from the same brain. PC in this case is the abbreviation for pedunculi cerebri. The question concerning the hypointense region in MRI antero-lateral to red nucleus is presently being studied in detail, applying this method to additional cases

Fig. 5. Cytoarchitecture x MRI

By combining both technologies, fundamental questions on post-mortem delay, appropriate fixation and neuroimagaing/neuropathological correlations could be addressed (Grinberg et al., 2008, 2009; Teipel et al. 2008).

The salient feature of this methodological approach to an atlas on the human basal ganglia is the post-mortem in situ MRI-scanning of the brain and the histological processing of the brain to generate serial 400 µm thick Nissl-stained sections. This protocol greatly facilitates cytoarchitectonic delineation of cortical and subcortical grey matter, compensation for shrinkage, and deformation and co-registration of high-resolution Nissl-stained sections with MRI scans.

Compelling results of match (red nucleus) and mismatch (subthalamic nucleus) of Nissl-stained sections with the MRI-boundaries are depicted in Fig. 5.

The images are imported to software tools and warped to the original MRI scans, following nonlinear and linear correction protocols developed by the team and yet to be published. Three-dimensional cytoarchitectonic contours can then be compared to the original scans. All the illustrations presented in this chapter were made using our own material and techniques.

5. Probabilistic atlases

Probabilistic atlases depict the normal range in size, shape, and topographical location of individual cortical or subcortical structures from many subjects. The rationale behind the idea is that the neuroanatomy of a select single subject's brain cannot cover the pronounced

anatomic variability. Consequently, errors in diagnosis and neurosurgical interventions impend on generalizing interrelationships of a single brain. Probabilistic maps can include features such as cytoarchitecture, chemoarchitecture, blood flow distributions, metabolic rates, behavioral and pathologic correlates, electrophysiologic tissue characteristics and others (Mazziota, 1995). Some previously described atlases list probabilistic features (Andrew et al., 1969; Afshar et al., 1978; Krauth et al., 2010). In this paragraph, special focus will be on probabilistic atlases not classified in previous sections.

5.1 A probabilistic atlas and reference system for the human brain: International consortium for Brain Mapping (ICBM)(Mazziotta et al., 2001)

Through an International Consortium for Brain Mapping (ICBM) a data set that includes 7000 subjects between the ages of eighteen and ninety years and including 342 mono- and dizygotic twins has been collected.

Data on each subject include detailed demographic, clinical, behavioral, and imaging information. DNA has been collected for genotyping from 5800 subjects. A component of the program uses post-mortem tissue to determine the probabilistic distribution of microscopic cyto- and chemoarchitectural regions in the human brain. This can be combined with macroscopic information about structure and function derived from subjects *in vivo*, providing the an opportunity to gain meaningful insights into the concordance or discordance in micro- and macroscopic structure and function (Mazziota et al., 2001).

5.2 A probabilistic functional atlas of the human subthalamic nucleus (Nowinski et al., 2004)

The concept of probabilistic functional atlas (PFA) was introduced by Nowinski. His idea is to overcome limitations of the current electronic stereotactic brain atlases, such as anatomical nature, spatial sparseness, inconsistency, and lack of population information. The PFA is an algorithm that converts the coordinates of the neurologically most effective contacts into probabilistic functional maps, taking into account the geometry of a stimulating electrode and the patient's anatomy. Nowinski published the use of this algorithm to build an atlas of the subthalamic nucleus and of the ventrointermediate thalamic nucleus (VIM) (Nowinski et al., 2004, 2006).

This paper introduces a method for generation and validation of a probabilistic functional brain atlas of subcortical structures from electrophysiological and neuroimaging data. The method contains three major steps: (1) acquisition of pre-, intra-, and postoperative multimodal data; (2) selection of an accurate data set for atlas generation; and (3) generation of the atlas from the selected data set. The method is here applied to construct the probabilistic functional atlas of the human subthalamic nucleus from data collected during surgical treatment of 184 patients with Parkinson's disease. It is based on preoperative X-ray ventriculography imaging, intraoperative electrophysiological measurements and X-ray imaging, and postoperative neurological assessment. This method can be used to build PFAs from other regions, as the next work from 2006 did.

5.3 A probabilistic functional atlas of the VIM nucleus constructed from pre-, intra- and postoperative electrophysiological and neuroimaging data acquired during the surgical treatment of Parkinson's disease patients (Nowinski et al, 2006)

This work addresses construction of the PFA for the ventrointermediate nucleus (PFA-VIM). The PFA-VIM is constructed from pre-, intra- and postoperative electrophysiological and

neuroimaging data acquired during the surgical treatment of Parkinson's disease patients. The data contains the positions of the chronically implanted electrodes and their best contacts. For each patient, the intercommissural distance, height of the thalamus, and width of the third ventricle were measured. An algorithm was developed to convert these data into the PFA-VIM, and to present them on axial, coronal, and sagittal planes and in 3D. The PFA-VIM gives a spatial distribution of the best contacts, and its probability is proportional to best contact concentration in a given location. The region with the highest probability corresponds to the best target. The authors content that the PFA-VIM atlas overcomes several limitations of the current anatomical atlases, and can improve targeting of thalamotomies and thalamic stimulations.

6. Discussion

Inserting electrodes and needles without direct visual control into a hermetically closed space, filled with complex and vital structures, sounds at the first sight at least dangerous. Stereotactic interventions allow a tiny margin of error, since coagulation of the wrong nucleus or finding a big vessel inadvertently with a small opening on the skull may result in immediate death or irreparable neurological damage. Mechanical devices were developed (Horsley & Clarke, 1908) to give the neurosurgeons the precision that their hands will never achieve. A version of the stereotaxic apparatus created by Horsley and Clarke was adapted by Spiegel and Wycsis to perform such procedures in humans. At that time, they realized that safe intracerebral navigation with minor side effects necessitates a precise brain map. In 1952 these authors published the first stereotactic atlas of the human brain, objecting that functional stereotactic neurosurgery ''requires an exact preoperative calculation of the electrode position, and such a calculation depends on two conditions: (1) determination of a reference point by means of an X-ray picture taken under definite standard conditions, and (2) an exact knowledge of the position of the area to be destroyed in relation to the reference point. Thus . . . a stereotaxic atlas of the human brain is presented'' (Spiegel &Wycis, 1952).Today, high-resolution images from the brain are possible; however, some important target regions are still hidden, and others are so far not subject to a precise morpho-functional delineation.

6.1 Correcting tissue processing-induced errors
The rationale for a stereotactic atlas is to unravel the position of certain brain regions that we cannot directly see with the current image technologies from the patient's cerebrum. In 1952, Spiegel and Wycis had to project their atlas into an X-ray picture. Today, we can count on much more refined images of the human central nervous system, like 3.0T MRI. As we will discuss later, even this detailed picture is not enough to show all the structures we are aiming to reach. Histological methods still supply the standard tools for identification of deep brain structures, be they neurons or fiber tracts. Conventional histology is applied to thin slices of brain tissue obtained from a diseased subject. The tissue is most often submitted to a formalin fixation (Yelnik et al., 2009).The processing of the nervous system leads to transformations in its size and form since the moment of death. Formalin fixation and other chemical reactions cause several volumetric changes in the nervous tissue. The changes in cerebral tissue due to fixation have been studied since the late 1960s (Bauchot, 1967) and the reliability of dimensions of formalin-fixed brains as well (Small & Peterson, 1982). The effects of formaldehyde on the human cerebrum have been described to result in a maximum increase in weight and volume between the first and fifth day, which decreases during the following weeks and months

(Fischer et al., 1973; Kato, 1939; Lagerlöf & Torgersruud, 1934; Stevenson, 1923; Treff & Kraus, 1960; Tutsch-Bauer, 1979 as cited in Quester & Schröder, 1997). This "positive formalin effect" (Schremmer, 1967 as cited in Quester & Schröder, 1997) is higher for lower formalin concentrations (Flatau, 1897; Treff and Kraus, 1960 as cited in Quester & Schröder, 1997).The results from Quester and Schröder (1997) confirm that local shrinkage and correction factors have to be determined for each area of interest owing to the heterogeneous constitution of the individual cerebral structures.

Embedding, sectioning, staining and mounting are likewise sources of tissue distortion. Each of these factors deforms the histological slice either in a homogeneous (linear distortion) or heterogeneous (nonlinear distortion) fashion. For example, the gray and the white matter have a differential staining shrinkage (Simmons & Swanson 2009; Kretschmann et al., 1982). In Schaltenbrand's study from 1977 (Schaltenbrand &Wahren, 1977) the average shrinkage rate for different applied methods was variable. Embedding in paraffin led to an average shrinkage of 30%, while celloidin shrank the tissue in 20%, wax in 5% and freezing in 1%. For this reason they chose freezing as method, but they noticed that when freezing is used there is no embedding material to hold the tissue together, causing parts to become dislodged and float around, especially those close to the surface.

In order to correct all these confounding factors, it is mandatory to know the precise volume and shape of the tissue prior to processing. Spiegel and Wycis used fiducial markers to guide them. Many years later, the fiducial concept was resumed by Yelnik et al. (2007), but with the great technological improvement of having the specimen scanned in a MRI scanner before the brain was removed. High-resolution post-mortem imaging provides important information about the volume and form of the brain before being processed (Pfefferbaum et.al, 2004) and it can be used to correct and align histological slices. In 1952 these corrections were performed by photographic manipulation, and within the following years this was the standard procedure. In 1987 Yoshida (Yoshida, 1987) focused on extracting a three-dimensional volume from the great histological slices obtained by Schaltenbrand and Bailey (Schaltenbrand & Bailey, 1959). In the following years, other authors created three-dimensional atlases based on the most-consulted printed atlases, using computational technology (Nowinski et al.,1997; St-Jean et al.,1998; Nowinski & Belov, 2003; Ganser et al., 2004; Carballo-Barreda et al., 2007). However, some inaccuracies on the original atlases led to great 3D inconsistencies (Nieman et al., 1994; Nowinski et al., 2006a, 2006b).The orthogonal plates from the Talairach & Tournoux atlas are not consistent and as a result a given point in the stereotactic space may have up to three different labels. Another example is that 3D structures reconstructed from the Schaltenbrand and Wahren atlas from 1977 are often distorted and sometimes have unrealistic shapes (Nowinski et al., 1997). To overcome this, some techniques were developed. Nowinski in 1997 (Nowinski et al., 1997) opted to correct by manual correction of rotation and overlay-plate mis-registrations; however, the inherent inconsistencies from the original templates could not be corrected. St-Jean in 1998 (St-Jean et al., 1998) addressed the problem first by performing an interpolation of the 2D contours using Hermite polynomials to achieve a 3D representation of the structures. The second step was registering the atlas volume to an MRI reference volume, the Colin27 (average of 27 scans from the same subject). This was made by identifying 250 homologous landmarks at the atlas and at the MRI and then applying the Brookstein thin-plate spline approach to warp them. As a result, the Colin27 was a labeled 3D volume based on the Schaltenbrand & Wahren atlas and could be warped to a given patient MRI with better accuracy. In 2003, Nowinski (Nowinski & Belov, 2003) added structures to the original templates to improve 3D consistency, and developed algorithms to reformat the atlas to the

intercommissural plane. In 2004, Ganser presented an algorithm to align and reconstruct three-dimensionally the Talairach and Tournoux atlas (Ganser et al., 2004). The authors therefore used the coronal plates and improved the spatial resolution by interpolating additional cross-sections between each pair of adjacent original plates. After processing the images with Delauney tetrahedrization of the object using the Nuages algorithm, smoothing the shapes by applying a spatial low pass convolution filter, extracting the surface representation of the object with the marching cubes algorithm (Lorensen and Cline, 1987 as cited in Ganser et al., 2004), and reducing the number of vertices by applying the polygon reduction algorithm proposed by Melax (Melax, 1998 as cited in Ganser et al., 2004), they obtained a better 3D surface from the Talairach and Tournoux atlas. The lateral symmetry of the brain gives rise to a high redundancy in brain cross-sections, for which reason Talairach and Tournoux drew only one hemisphere in detail. They exploited this symmetry for further reduction of data as well: They have only processed the right hemisphere of the atlas and mirrored it at the midsagittal plane to the left side.

Even with all the mathematical treatment and computation of the images, the 3D atlases based on the classical 2D atlases did not fully satisfy the functional neurosurgeon's needs. Therefore, three groups started building three-dimensional atlases based on own histological preparations, so they could cut and prepare the slices using modern technique.

Even with new methods, the slices continue to suffer linear and nonlinear transformations by the fixation and processing techniques. The Canadian group (Chakravarty et al., 2006) used a previously presented nonlinear transforming algorithm (ANIMAL-Automated Nonlinear Image Matching and Anatomical Labeling) to register and align slice-to-slice together to build a contiguous 3D histological volume. The French group (Yelnik et al., 2007) used MRI scans from the same subject and slice-to-slice alignment (crioblock corregistered to cryosections, Nissl, immunostained, T1 and T2 MRI images) to build the coherent volume. The corresgistration was made with software tools (TTS, YAv++ and BALADIN) through an intensity-based block-matching approach. The Swiss group (Krauth et al., 2010) calculated the distortion index of the tissue by measuring the ICL distance in MRI *in vivo* and *in vitro,* and comparing it with the ICL distance from the processed tissue. They extrapolated the results to the stacks in which no MRI was performed.

In fact, the use of MRI scans as parameter to align and correct tissue processing linear and nonlinear transformations is the gold standard at the moment; however, the methods so far used to readapt the histological slices into their original volume and form can be further developed to allow exact correlations between histology, immunostaining, and image.

The next challenging part of the process is how to adapt this histological 3D coherent volume obtained to a given patient.

6.2 Warping the atlas to the patient

As soon as we have consistent, validated, three-dimensional surfaces, we have to fit them into the patient's brain. Therefore, reliable (and visible in both atlas and patient image) reference points are needed to transform the atlas into the living brain ($\mathbb{R}^3 \rightarrow \mathbb{R}'^3$ transform). In the early 1950s, pneumoencephalography and ventriculography permitted the visualization of some intraventricular landmarks as the pineal gland calcification, habenular calcification, and ventricular landmarks (AC and PC). Based on this, Spiegel and Wyics developed the first intracerebral coordinate system used in their atlas. An imaginary line connecting the center of the PC with the pontomedullary sulcus at the posterior border of the pons (PO) defined the CP-PO line.

This system was not really easy to employ, so they and others have developed simpler and more useful ones. Talairach could prove a good and consistent relationship between the AC-PC line (and its derivative planes) with the deep brain nuclei (Talairach et al., 1957). This would change the standard for intracerebral localization. In their 1988 work Talairach & Tournoux present the proportional grid system, which permits the transformation of the models to fit individual variability.

These deformations can be performed using different strategies, as landmark-based deformation methods or automatic deformations based on registration algorithms.

The most widely used system to adapt a brain atlas to the individual anatomy of a living subject is the proportional system of Talairach. It relies primarily on the AC-PC distance, i.e., the length between the anterior and posterior commissural points, well-identifiable on a ventriculography or a mid-sagittal section of a MRI acquisition. The user has just to measure the AC-PC distance in the living brain and to adapt the antero-posterior length of the atlas to that of the brain. The proportional system of Talairach is a reliable system, although it is inhomogeneous since the adaptation along the antero-posterior dimension is based upon two deep brain ventricular landmarks, whereas adaptation along the medio-lateral and infero superior dimensions depends on the overall size of the cerebral cortex. This is due to the fact that with ventriculography, internal landmarks are less clear along these dimensions the height of the thalamus and width of the third ventricle are the best possible landmarks (Yelnik, 2009).

An automatic registration algorithm is based on the comparison of features (grey-level values, points, lines, graphs, etc.) present in the two images to be registered. The algorithm is defined by three main characteristics: the similarity measure, the space of allowed deformations (the number of degrees-of-freedom (DoF) of the deformation, e.g., 6 DoF for a 3D rigid transform), and the optimization method that is used. Deformations can be very constrained (limited number of DoF), e.g., linear scaling (7 DoF) or not, like elastic, fluid, or even free-form deformations. These last types of deformations are often referred to as morphing or warping transforms. The choice of the most adequate deformation type is important, as it directly influences the quality of the atlas-to-patient result.

Chakravarty, in 2009, has studied and compared the "atlas to patient warping techniques"(Chakravarty et al., 2009) describing and comparing the linear, piece-wise linear and nonlinear techniques. These are automatic developed algorithms, although in the piece-wise technique, twelve different landmarks must be identified on both atlas and patient data, performing a Talairach transformation.

Chakravarty resumes the most typically used methods to warp the atlas to patient MRI data in two. The first is matching the anatomical structures directly from the atlas to the same structures seen in pre-operative scans (Ganser et al., 2004; Nowinski et al., 2000; Xu & Nowinski, 2001 as cited in Chakravarty et al., 2009). The second method starts with a set of anatomical atlas contours, pre-aligned to an MRI template. A transformation is then estimated between the template MRI and patient's MRI. Once this template-to patient transformation is estimated, the transformation is then applied to the anatomical atlas contours, thus customizing it to patient's anatomy (Bardinet et al., 2005; Chakravarty et al., 2005; D'Haese et al., 2005; Sanchez Castro et al., 2006; Yelnik et al., 2007as cited in Chakravarty et al., 2009).

6.3 Do we need new atlases?

Currently, magnetic resonance imaging is the method of choice for anatomic delineation of the brain. Its noninvasive nature allied to the possibility of unlimited repetition provides the

option of *in vivo* applications for clinical purposes and basic science research with quite comfortable accessibility. Volumetric and multi-sequence acquisitions of MRI images supply different sets of data, for instance, macroscopic anatomy, differentiation of gray and white matter, detection of iron deposits, fiber tracking, spectroscopy, BOLD effect in addition to the possibility of re-slicing and generating 3D reconstructions of the brain. It is even possible to differentiate the cortical layers in MRI (Fatterpekar et al., 2002). However, the protocol used to achieve this definition was a 9.4 T machine and each specimen was submitted to an overnight acquisition time of 14 hours and 17 minutes. This is not possible in living patients, not only because of the long acquisition time, but also due to movement artifacts including breathing.

The subthalamic nucleus is a good example for this discussion, because it is an important target to place electrodes in Deep Brain Stimulation (DBS) for treatment of Parkinson's disease, (Limousin et al., 1995; Benabid et al., 2001; Hamani et al., 2004) dystonia and epilepsy, and obsessive-compulsive disorders (Mallet et al., 2002).The real limits of STh within the hypointense image in the region lateral to the red nucleus is still matter of debate (Littlechild et al., 2003; Pollo et al., 2003; Dormont et al., 2004 ;Andrade-Souza et al., 2005 ; Sather & Patil, 2007; Stancanello et al., 2008; Kitajima et al., 2008;Caire et al., 2009; Vertinsky et al., 2009).The problem seems bigger if we consider that most neurosurgery services use 1.5 to 3.0 T magnetic fields in MRI acquisition. Although MRI images have improved in recent years, no sharp limits are really observed. Additionally, the iron content of the nucleus is unevenly distributed, predominating in its anterior aspects. We cannot forget as well the artifacts such as partial volume effect that distort the images and blur the nuclear outlines when we target small volumes (Ballester et al., 2002). On the other hand, the pioneer experiences of the first atlases based in brain histology have recently obtained substantial   improvement   with   the   addition   of   new   staining   techniques, imunohistochemestry specific to different subcellular and membrane structures of neurons and glial cells, and the development of softwares and algorithms to warp and correct the errors induced by tissue processing, all of which have made it more reliable and precise. Functional neurosurgery is aimed at functional targets, but these functional units are linked to an anatomical substrate. If we can in the future overlap the cytoarchitecture, intraoperative electrophysiology, and high-resolution functional images, we will surely be able to better understand the function and structure relationship and propose new treatments for diseases that have seemed hopeless until now .

7. Future perspectives

The future directions of image-guided neurosurgery include coherent 3D histological and histochemical volumes which can be interactively visualized and precisely warped to a given MRI scan. Templates and 3D reconstructions should be in electronic format and available over the internet , with a user-friendly interface that allows neurosurgical planning and better understanding of complex brain structures and spatial and functional relationships.

8. Conclusion

The field of neurosurgery-driven brain localization is still open and growing. Technological progress will greatly improve the precision of brain targeting. Atlases are an important part of this process, and together with the developing brain imaging methods and electrophysiology, future works will open new frontiers to the knowledge of the human brain as a whole.
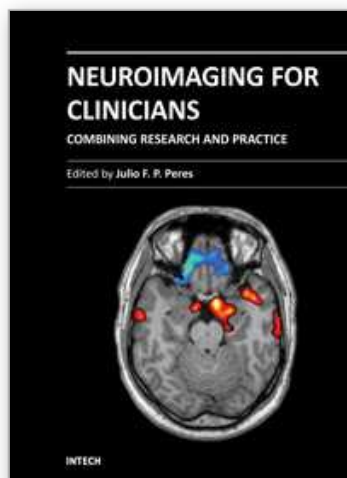
9. Acknowledgment

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Neuroimaging for Clinicians - Combining Research and Practice

Edited by Dr. Julio F. P. Peres

Neuroimaging for clinicians sourced 19 chapters from some of the world's top brain-imaging researchers and clinicians to provide a timely review of the state of the art in neuroimaging, covering radiology, neurology, psychiatry, psychology, and geriatrics. Contributors from China, Brazil, France, Germany, Italy, Japan, Macedonia, Poland, Spain, South Africa, and the United States of America have collaborated enthusiastically and efficiently to create this reader-friendly but comprehensive work covering the diagnosis, pathophysiology, and effective treatment of several common health conditions, with many explanatory figures, tables and boxes to enhance legibility and make the book clinically useful. Countless hours have gone into writing these chapters, and our profound appreciation is in order for their consistent advice on the use of neuroimaging in diagnostic work-ups for conditions such as acute stroke, cell biology, ciliopathies, cognitive integration, dementia and other amnestic disorders, Post-Traumatic Stress Disorder, and many more

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