Obstetric brachial plexus lesions

To The Editor: We would like to comment on the paper by Pondaag et al. (Pondaag W, van der Veken LPJ, van Someren PJ, et al: Intraoperative nerve action and compound motor action potential recordings in patients with obstetric brachial plexus lesions. J Neurosurg 109:946–954, November, 2008). We have only operated on 16 neonates with obstetric brachial plexus lesions (OBPL) taken from a group of 171 who were referred for possible surgical reconstruction. The majority of these patients showed substantial clinical improvement without surgery over the course of many months after birth and were not candidates for surgery. In addition, we have operated on a large number of adult patients with stretch/avulsive injuries. We agree that there are significant differences between infant brachial plexus stretch injuries due to birth OBPL and adult stretch/contusive lesions to the plexus. However, we do not believe that the underlying pathophysiological mechanisms are so different that operative recordings would be invalidated in one scenario and not the other. Based on our own limited experience of neonatal OBPLs combined with a more extensive experience in the adult population, we have determined that there are 5 major categories of recording patterns in stretch injuries and operative neurophysiological findings.

Recording Patterns in Stretch Injuries

1) Normal nerve action potential (NAP) is recorded from a normal spinal element and its outflow (often C-7 or C-8). Compound motor action potentials (CMAPs) with good amplitude of response and conduction velocities of 50–70 m/second are observed.

2) Small and slowly conducted NAPs are seen in an injured spinal element with continuity and good regeneration (axonotmesis, Sunderland Grade II or III). A regenerative NAP is usually small and of low amplitude, has slow conduction (20–40 m/second) and is usually distinct from the stimulus artifact. The response is always reproducible on sequential recordings. There may or may not be an evoked CMAP depending on the time between injury and when the recording is done. Sometimes, it will be positive in OBPLs for biceps or triceps after 9 months or more if the lesion to the element was complete to begin with, or of course sooner if the injury was incomplete to begin with.

3) Normal-appearing NAPs are recorded with avulsion that is purely preganglionic. There is an NAP with good amplitude and conduction velocity of a normal or even greater velocity. Evoked CMAPs are usually absent unless stimuli spread to adjacent elements without preganglionic injury. This NAP is positive because the injury is solely to sensory axons prior to the dorsal root ganglion (DRG). As a result, the wallerian process does not affect those axons beyond the DRG or along any of their more distal course. This NAP can be distinguished from a regenerative one by its larger amplitude and much faster conduction either at or above normal limits and especially by the fact that one can record it well distal to the clavicle (for example, from musculocutaneous, axillary, or radial nerves) at a point in time (3–12 months postinjury) when sufficient new axons and thus a regenerative NAP could not have been expected to reach those levels. The CT myelogram or MR image is often positive for a meningocele or other abnormality but not always. Of great importance, exploration, even at a foraminal level, does not always show grossly intact axons and/or DRGs. Inspection of spinal nerves and trunks may appear intact, but not always because there may be a degree of more lateral injury, although not enough to completely destroy the spinal sensory axons.

4) A flat NAP trace can be due to pre- and postganglionic injury in which, despite the preganglionic injury, there is a neuroma-in-continuity involving the spinal nerve, trunk, or even divisions. Because of the postganglionic portion of the injury, there is no or little preservation of axons, even the sensory ones, and thus no conducted NAP. There is no evoked CMAP unless adjacent or nearby less involved elements have stimuli transmitted to them and thence to muscle. Sectioning proximally on such a spinal nerve usually shows either gross evidence of avulsion or heavy scar, and in any case it is not a useful structure from which to lead out grafts.

5) A flat NAP trace can be due to a neurotmetic (Sunderland Grade IV) lesion-in-continuity lateral to the root at spinal nerve and upper trunk levels. Evoked CMAPs will usually be absent unless less involved elements with connection(s) to muscle(s) being tested are stimulated. In the occasional case, a small number of fibers may successfully penetrate the lesion and reach muscle. However, the flat NAP trace produced by insufficient numbers of regenerating axons is not likely to be followed by a successful return of adequate function. In fact, these few regenerated fibers may provide a misleading impression when they are all synchronized by stimulus pulses and produce visible muscle contractions or a clear CMAP. It takes only a few fibers reaching muscle to evoke a recordable CMAP or even to mediate a visible contraction.

There needs to be recognition of some of these differences when data are presented about plexus stretch lesions. This is especially so for Items 3 and 4 above. Failure to recognize these differences could lead to mistaken analysis. For example, a flat trace across a lesion could, if the lesion is lateral to the root, be due to neuromatosis and lead to resection and repair with some hope of recovery as recognized by the authors.

On the other hand, if the flat trace is due to a pre- as well as postganglionic lesion, resection and direct repair will be of no value. A CT myelogram will not always be abnormal at such levels. Neurolysis of an element conducting an NAP due to retained sensory fibers because of a preganglionic lesion with some more lateral damage also does not result in function. Timing is also impor-
tant. Neurolysis without resection of an element having a conducted NAP and distal CMAPs at a year or more postinjury may not suffice.

In the 16 cases of OBPL at Louisiana State University Health Sciences Center that were surgically treated because of poor biceps and/or shoulder abduction ≥ 10 months after birth, NAP studies were performed on exposed elements and 96 recordings were made. This resulted in 30 elements having a neurolysis due to positive recordings, 19 having grafts due to negative traces in which there was no operative evidence of avulsion, and normal preoperative CT myelograms at those levels. Each of the resected specimens was Sunderland Grade IV histologically. Ten nerve transfers were due to preganglionic or pre- and postganglionic traces combined with surgical inspection. Usually, but not always, there were abnormal CT myelographic findings at those levels.

Surgical Inspection

It is claimed that one can tell whether a root is avulsed in the operating room, and such is the case when DRG is seen outside the foramen. However, there can be significant preganglionic avulsion without such a finding even if the CT myelogram is negative at that level. Then, if the surgeon is unaware of what a preganglionic NAP looks like, he or she will assume that there are good regenerative axons and axonotmesis or sparing and perform neurolysis on an element in which, because of more proximal irreversible injury, there is no hope of recovery. Purely, preganglionic lesions are not always accompanied by normal-appearing distal elements, although such is often the case. Distal elements can be thickened and swollen and still contain preserved sensory fibers. The more severe axonotmetic lesion (especially a Sunderland Grade III) can be swollen and firm and appear quite scarred on gross inspection, causing difficulty in discerning the fascicular continuity, just as the neurotmetic one (Sunderland Grade IV). The ability to determine fascicular continuity by gross inspection, even with magnification but without internal neurolysis is, in the typical neurona, impossible. Even with internal neurolysis, fascicular continuity through the lesion does not insure recovery because fascicular damage itself may be neurotmetic, especially with stretch injuries.

Technical Considerations

As pointed out by the authors, the infant plexus is small and relatively short, so direct recordings are technically difficult and need to be very precise. However, such recordings are less useful when the time base is > 0.5 msec/division. In the recordings in this paper, the time base for NAPs was 2 msec/division.

Because the study was done in infants, only a 3–4-cm distance was used for stimulation and recording studies. That setting does compress the stimulus artifact, but it also makes it more likely that an NAP will be enfolded within the stimulus artifact. When relatively short distances are used for recording, as was the case here, the time base should be set on 0.5 msec/division or at most, 1 msec/division, but not a 2 msec/division except when stimulating and recording over longer distances. Stimuli also need to be brief (≤ 0.05 msec in duration) not only to reduce stimulus artifact, but also because longer-duration stimuli can activate small, poorly myelinated fibers that may or may not eventually become large enough to produce useful function.

The authors claim that the waveform marked initially in Fig. 2A is an NAP. If so, that would have a latency of 4 msec and if recorded at 3 cm a velocity of only 7.5 m/sec and, if recorded at 4 cm, only 10 m/sec, so it is not a good example of an NAP, especially in the later months after the birth injury when these recordings were done. But is it really an NAP? It is more likely to be stimulus artifact overrun and not an NAP. What follows the NAP shown would, if it is truly an NAP, be 6 m/sec if recorded at 4 cm and 4.3 m/sec if recorded at 3 cm. If the 60-cycle notch filter was left on on the recording machine, such a false response and the waves that follow could be recorded. That secondary wave could also be a muscle action potential (MAP) picked up by the NAP recording electrodes in some settings; such an MAP is possible when muscle is directly recorded and yet there is an absent NAP. This is because it only takes a few fibers reaching muscle to evoke a recordable CMAP, but it takes several thousand moderate-sized fibers across a lesion to record a true NAP. Thus, in normal nerves, 18 of 18 recordings were positive as seen in their Table 3. In lesions believed to be “axonotmetic” on inspection, despite the difficulties of being certain of that diagnosis, 112 of 114 traces were positive, so in that setting, NAPs appeared to be at least, as the authors found, accurate.

The NAP recordings appear to fail in their hands in what they describe as “neurotmetic” lesions (53 of 373 lesions had positive NAPs), whereas the others were flat, fitting better with a neurotmetic lesion. Were some of these “neurotmetic” lesions falsely resected Sunderland Grade III lesions in which the element can be swollen and scarred? Their text suggests no. Perhaps some of these lesions had a preganglionic as well as a postganglionic axonotmetic lesion and were swollen and scarred lateral to the foramen. When a recording is classified as absent, it may mean either that the CMAP was absent biologically or that it could not be recorded. To exclude the latter, it is often helpful to record from a segment of known normal nerve or plexus element. This ensures that all technical considerations are present for a successful recording. Unfortunately, the authors emphasize their observation that 28 of 62 traces on elements believed to be more proximally avulsed had positive NAPs. However, this is exactly what one would expect because a significant proportion of avulsions, not only in adults, but also in infants, are purely preganglionic and thus have distal sensory fiber sparing and therefore paradoxically have a positive NAP, which is possible despite a negative myelogram at that level.

Differences Between Birth and Adult Stretch Palsies

Despite these observations, we agree that there is no question that most infant brachial plexus stretch injuries due to birth OBPL differ from adult stretch/contusive lesions to the plexus. The infant palsies are usually less severe axonotmetic lesion and were swollen and still contain preserved sensory fibers. The more severe axonotmetic lesion (especially a Sunderland Grade III) can be swollen and firm and appear quite scarred on gross inspection, causing difficulty in discerning the fascicular continuity, just as the neurotmetic one (Sunderland Grade IV). The ability to determine fascicular continuity by gross inspection, even with magnification but without internal neurolysis is, in the typical neurona, impossible. Even with internal neurolysis, fascicular continuity through the lesion does not insure recovery because fascicular damage itself may be neurotmetic, especially with stretch injuries.
vere and more likely to recover spontaneously and therefore are less likely to need surgery, at least on the plexus itself. Even those elements that are surgically treated are more likely preoperatively to have some electromyography (EMG) evidence of sparing or partial recovery. This may be due at birth from input from C-7 not only to the biceps muscle, but also to the deltoid muscle. It could also be due to differences in EMG sampling densities between infants and adults or even more central, organizational considerations. We suspect some OBPL neuromas in continuity do have some axons spared from the beginning and/or a more robust early axonal regeneration than most adult stretches.

Despite this supposition, reliable early clinical signs of effective spontaneous recovery from C-5 and C-6 by comparison with those from C-7 are often quite delayed, much more so than in adults. Finally, birth injuries predominantly involve C-5, C-6, and C-7 and upper and middle trunks without serious or at least persistent involvement of the lower elements. Thus, the incidence of persisting flail arms is less in the OBPL category than in the adult stretches.

Other studies using CMAPs but not NAPs to evaluate infant lesions-in-continuity have favored resection rather than neurolysis. One study in a very small cohort of patients used NAPs, but placed 1 of their 5 patients in the neurolysis category who had CMAPs but negative NAPs across the lesions-in-continuity.

In summary, we disagree with the conclusion that OBPLs cannot be accurately diagnosed at the time of surgery using the method of stimulation and recording CNAPs. When these recordings are timed appropriately, they provide the same information obtained in the adult population. We do agree that this method is particularly difficult in a neonatal population, and special consideration must be given to technique. These authors have taken the first step in an effort to apply this method to the pediatric population, and they are to be praised for their efforts. Hopefully, improved instrumentation and technique can be developed for use in the pediatric population that will permit the same principles of decision-making that we have learned for the adult population.

References

Response: We read with interest the letter of Drs. Kline and Happel in reaction to our paper.

At present, there is much controversy regarding the treatment of patients with OBPL. The most important issues concern indication, timing of surgery, and outcome measurements of treatment. Additionally, there is no clear consensus on the intraoperative surgical decision-making process.

Dr. Kline introduced intraoperative NAPs in the early 1970s to provide a rationale for the discussion on whether to leave the nerve (neurolysis) or cut and graft. Because of his strong arguments and data concerning NAP measurements in adult traumatic lesions, we applied this technique to infants with OBPL. Our hope and estimation was that this technique could provide us with information to facilitate the intraoperative assessment of an OBPL lesion-in-continuity.

We performed a prospective study in a consecutive series of 95 patients with OBPL, in whom surgery was performed at 4–5 months of age. All measurements were performed in a standardized way, and care was taken to avoid any technical errors. Blinded for the results of these measurements, lesions were classified as axonotmesis, neuromatosis, or root avulsion. From our study and large data set, we found a considerable overlap between the axonotmesis, neuromatosis, and avulsion groups. The conclusion we have drawn from our study is that NAP/CMAP measurements in infants with OBPL who are 4–5 months old does not allow for discrimination between axonometric, neuromatetic, and avulsive injuries.

We acknowledge and recognize the technical difficulties that Drs. Kline and Happel mention, and we gave them our full attention in the presented study. We believe, however, that the pathophysiological differences between adult and obstetric lesions will remain the most important factor instead of technical issues.

The presence of an NAP (or even a CMAP) did not correspond with the surgical and histological diagnosis of a favorable lesion. In this respect intraoperative neurophysiology proved too optimistic, just as diagnostic EMG seems to be in this group of lesions. Perhaps, as Drs. Kline and Happel have suggested, in OBPL neuromas-in-continuity some axons were spared from the beginning, or they have recovered by the time of EMG or surgery. Maybe such a small number of axons are sufficient to provide an NAP, or even a CMAP, but in clinical practice this limited axonal regeneration will not lead to satisfying clinical recovery.

Our conclusion accounts for only when the NAP/CMAP measurements are performed in the settings we described. We cannot exclude the possibility that technical refinements or improvements may ultimately make the technique a valuable contribution to the intraoperative decision making process. We believe, however,
given the thorough attention we have given to all technical aspects and the profound overlap in measurements that it is not very likely to become of any value. (DOI: 10.3171/2009.3.JNS0977)

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Reference

Hydrocephalus in unruptured brain arteriovenous malformations

To The Editor: I read with great interest the recent article by Geibprasert et al. (Hydrocephalus in unruptured brain arteriovenous malformations: pathomechanical considerations, therapeutic implications, and clinical course. Clinical article. J Neurosurg 110:500–507, March, 2009).

Hydrocephalus due to unruptured brain arteriovenous malformations (AVMs) is a rarely described entity. However, in high-volume centers these cases are seen once in a while, and this publication is important to focus attention to its management. The discussion of pathophysiology of hydrocephalus in AVMs through obstruction of CSF pathways (obstructive hydrocephalus) is comprehensible as well as the hypothetical venous outflow obstruction, which may lead to a venous congestion and consequent impaired CSF resorption (malresorptive hydrocephalus).

The authors accurately describe the potentially harmful overdrainage that may occur especially in AVM-associated hydrocephalus if patients are treated with a ventriculoperitoneal shunt, increasing the transmural pressure gradient of AVM vessels as well as leading to slit ventricles and subdural effusions. Modern hydrocephalus treatment modalities, which can reduce the risk of overdrainage, however, were not discussed.

In cases of obstructive hydrocephalus, endoscopic third ventriculostomy would be the treatment of choice for aqueductal compression as long as no AVM vessels interfere with the perforation site. For unilateral blockage of the foramen of Monro (as in Case 4 of the article), endoscopic septum pellucidotomy would be the first-line procedure.

In cases of malresorptive hydrocephalus due to secondary venous outflow obstruction, a ventriculoperitoneal shunt with a gravitational device should be used to prevent overdrainage. Overdrainage occurs when the patient is in an upright position due to the large hydrostatic difference between the ventricles and the peritoneum (frequently higher than 300 mm H₂O). High-pressure settings of simple programmable differential valves (here: 160 mm H₂O) do not prevent overdrainage, but result, additionally, in underdrainage when the patient is in a horizontal position. Much more effective are gravitational valves—as, for instance, a gravitational Miethke valve with a “5/30 setting”: when the patient is in a vertical position, overdrainage is protected through the high setting of 30-cm H₂O, whereas in the lying position the 5-cm–H₂O setting is active, resulting in much more physiological drainage. Overdrainage leads to reduction of ventricle size (to the point of slit ventricles), provoking chronic subdural hematomas. On the other hand, contact between the ventricle walls and catheter perforations may lead to secondary shunt occlusions. These mechanisms explain the high complication rate reported in the publication of Geibprasert et al., complications which might be even more harmful in AVM-associated hydrocephalus, as pointed out by the authors.

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Response: We would like to thank Dr. Kehler kindly for his comments on our manuscript regarding hydrocephalus in unruptured brain AVMs.

We are very grateful for his important remarks concerning hydrocephalus treatment modalities that may go along with a reduced risk of potentially harmful overdrainage in the above-mentioned clinical condition. Treatments such as endoscopic third ventriculostomy and implantation of programmable valves and shunts with gravitational devices will lead, when properly used, to a reduction in the complication rate of hydrocephalus in unruptured AVMs. (DOI: 10.3171/2009.4.JNS09488)

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Atlases for deep brain stimulation

To The Editor: I have read with great interest the article by Bardinet and coauthors (Bardinet E, Bhattacharjee M, Dornmont D, et al: A three-dimensional histological atlas of the human basal ganglia. II. Atlas deformation strategy and evaluation in deep brain stimulation for Parkinson disease. Clinical article. J Neurosurg 110:208–219, February, 2009). This is an important development in stereotactic and functional neurosurgery. In one of my earlier papers in Acta Neurochirurgica 2008, I called this work a “promising effort.”

However, in my opinion, this recent article has several misconceptions and incorrect statements that I believe should be clarified. The authors claim, “Probabilistic atlases have also been developed but these are mainly intended for work within the cortical sulci of the cerebral cortex.” This statement is incorrect. In collaboration with Dr. Benabid, I created a probabilistic functional atlas (PFA) for stereotactic and functional neurosurgery, and built PFAs for the subthalamic nucleus (STN) from 184 patients with Parkinson disease and 168 bilateral cases as well as for the nucleus ventralis intermedius from 107 cases. We also developed a portal for PFA building over...
the Internet.7 Our results have been published in several journal papers (Neurosurgery,9 Stereotactic and Functional Neurosurgery,12,13,18 Neuroimage,5,6 and Neuroinformatics). A clinical version of the PFA on CD-ROM is distributed by Thieme.17 The authors neglected our work, even though they included our paper published in Neurosurgery9 in their bibliography but commented on it from a peripheral perspective.

Another aspect is a comparison of the Bardinet et al. atlas with the Schaltenbrand and Wahren (SW) microseries.19 This comparison needs clarification to avoid misinterpretation. First, there is not a single SW atlas, but 3 SW microseries derived from 3 different hemispheres forming 3 SW atlases in axial, coronal, and sagittal orientations. Consequently, these 3 SW atlases are not consistent among themselves, which is their intrinsic feature and not a limitation. Any comparison to the SW atlases should specify which SW atlas (orientation) is being considered.

Second, any direct comparison to a print version of the SW is not quite fair. There is an electronic version of the SW atlases created by us (and also published by Thieme) called Cerefy12,16,17 which is substantially enhanced from its print edition.19 Moreover, a 3D version of the Cerefy atlas has also been created, allowing atlas images to be generated at any location and orientation. It should be noted that the Cerefy atlases have been accepted by the neurosurgical community.4,11 They are installed in more than 1500 neurosurgical workstations and licensed to several image-guided surgery companies, including Medtronic, BrainLab, Elekta, Renishaw, Prosurgic, and SurgiVision. Finally, we continuously study properties and provide enhancements to the SW atlases.2,13–15 Our efforts have been summarized in a recent book chapter.1

Third, the authors claim that: “...SN [substantia nigra] … traced as open (thus incomplete) contours in the SW atlas and completely defined in our 3D atlas.” This is not correct. The SN is traced as closed (thus complete) contours in the SW coronal atlas. Moreover, it is additionally parcellated into pars compacta and pars reticulata (Plate Fp – 3.0 [that is, a coronal plate 3 mm posterior to the midcommissural point]), while this parcellation is missing in the atlas by Bardinet et al. In general, many contours are closed in the electronic Cerefy version of the SW atlases.16

Fourth, although the atlas by Bardinet et al. uses the high-quality, high-resolution original data, this quality is diluted in the postprocessing. Substantial distortions resulting from freezing and cutting are compensated by warping against 1.5-T medium resolution and quality images (of 1.3 mm slice thickness for T1-weighted and 2.0 mm for T2-weighted images). For instance, the original AC-PC (anterior commissure–posterior commissure) distance of 23.2 mm became 24.4 mm after postprocessing. Moreover, the subdivision of the STN is based on animal studies. The fornix and ventricles were reconstructed from, and the STN, red nucleus and SN were verified with, the T2-weighted image.

Fifth, the authors claim that a high-accuracy automatic atlas performs data warping (in 10 minutes/hemisphere), amounting to 1-mm accuracy in the STN and 1–3 mm laterally. It should be noted that warping exploits an affine transformation that is unable to accurately compensate for the AC-PC distance, or the width of the third ventricle or internal capsule.

Sixth, the atlas of Bardinet et al. has about 80 structures (the index is not provided), and new emerging targets are probably missing. The original SW atlases (microseries and macroseries) have about 600 structures, and the Cerefy version 375 structures (microseries).16 Therefore, the SW atlases have a much finer parcellation and are more detailed.

Having spent nearly 2 decades on constructing electronic brain atlases, I do not claim that the SW atlases are perfect. We have studied the limitations of the SW atlases and published them earlier.1,13–15 In one of my previous papers1 I stated, “The SW probably needs the most urgent replacement,” which has yet to come. It should be noted, however, that despite their shortcomings, the SW atlases continue to be proven, highly valuable, and useful clinical tools for neurosurgeons.

In summary, the authors should be congratulated for their technologically advanced work and new entry into the portfolio of neurosurgical atlases. I believe that putting their work in a suitable perspective against the state of the art is important for the neurosurgical community.

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ed from pre-, intra- and postoperative electrophysiological and neuroimaging data acquired during the surgical treatment of Parkinson’s disease patients. Stereotact Funct Neurosurg 83:190–196, 2005


Response: We have examined carefully the long commentary of Prof. Nowinski whom we thank for attentive reading of our work but who suggests that our article “has several misconceptions and incorrect statements.”

In our article, we described a computer-based procedure with which an anatomical atlas of the human basal ganglia can be deformed to fit the specific geometry of the brains in individual patients.

The construction of this atlas, published in 2007, was based on a postmortem brain specimen that was processed for histological analysis from which basal ganglia contours were traced. This atlas has 2 specific characteristics. It consists of 3D meshes that come from histology and can therefore be sectioned in any given plane, and it is automatically adapted to the brain of a given patient by MR imaging coregistration using appropriate algorithms.

There are many other computer-based atlas approaches in the literature, but our article, primarily devoted to the deformation strategy of our anatomical atlas, did not intend to provide a thorough analysis of existing atlas approaches (Textbook of Stereotactic and Functional Neurosurgery has just been published in which several chapters, including our own contribution and that of Prof. Nowinski, are devoted to such reviews). In our state-of-the-art discussion, we focused on 3 groups (led by senior authors Peters, Dawant, and Collins) who developed computer-assisted methods for planning and guidance in deep brain stimulation (DBS) procedures, including atlases of the basal ganglia that were deformed on patients using fully automatic and nonrigid image registration algorithms. As a consequence, the otherwise important PFA of Profs. Nowinski and Benabid was not included in this part of the discussion, but in the Atlas Deformation section in which we considered the PFA a semiautomatic landmark-based deformation method.

There are 3 main topics in Prof. Nowinski’s commentary.

Comparison With the SW Atlases

In the past, we used the coronal and axial series of this atlas, which indeed remains a highly valuable and useful tool for neurosurgeons to localize stimulating electrodes in parkinsonian patients. The semiautomatic and landmark-based trilinear method that we used for atlas/patient coregistration provided satisfactory results. However, observing the inconsistency of the 3 atlas microseries in 3D and their very irregular interslice spacing urged us to develop a truly 3D histological atlas of the basal ganglia. As explicitly indicated in the present article, we compared the axial series of the SW atlas (p 212, fourth paragraph) with our 3D meshes after sectioning them in the SW axial plane to show that they did not differ significantly.

Characteristics of Our Atlas

In his commentary, Prof. Nowinski questions the quality of our atlas. As the atlas construction was specifically developed in our previous paper, we invite the reader to refer to the paper by Yelnik et al. Regarding the “postprocessing,” original data were actually high-resolution data but were, as any histological material, subject to distortions. Using the MR imaging acquisition of the same brain to reconstruct histological data in 3D allowed us to correct for these distortions (such as shrinkage). The increase of AC-PC distance from 23.2 to 24.4 mm is a typical example of the usefulness of this correction. Fusion of the histological and MR imaging data allowed us to integrate the high level of definition histology onto the MR image of the atlas, providing a real 3D histology.

In our atlas we did not include topographic subdivisions as the dorsal and ventral subdivisions of thalamic nuclei, and we did not include structures present in the SW atlases, such as the amygdala and hypothalamic subnuclei. The 80 structures that have been traced comprise the nuclei and fiber bundles that are targeted during the DBS protocols to which we adhere for Parkinson disease, dystonia, OCD, Gilles de la Tourette syndrome, tremor, and depression, but also those that can potentially be involved by the diffusion of the stimulating current.

Automatic Atlas Deformation

The deformation strategy used in this study has been defined by Dr. Bardinet and the Epidaure project at INRIA, Sophia-Antipolis, France, both specialists in image processing algorithms. This strategy is a hierarchical pipeline that comprises affine transformations computed on regions of interest including the basal ganglia. It has been selected among several other deformation procedures.
(for example, elastic or fluid deformations) because it provided the best compromise between over-constrained deformations as an AC-PC-based linear transformation and free-form deformations that did not preserve the known anatomy of the basal ganglia. This strategy was carefully evaluated, and we concluded that a 1-mm accuracy for target localization was achievable with this atlas.

Our atlas is currently in use in several clinical multicentric DBS protocols in which it has provided convincing anatomoclinical results.2,9–11 However, using the Cerefy electronic version of the SW atlases developed by Prof. Nowinski remains, of course, an alternative possibility whose qualities, which have been extensively developed in his commentary and the aforementioned chapter, are well known. (DOI: 10.3171/2009.8.JNS091004)

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References


Erythropoietin and subarachnoid hemorrhage


We congratulate the authors on completing this study. The paper is interesting and timely because prior evidence predicts a protective effect of erythropoietin (EPO) on ischemia following SAH. In this regard, we first showed a beneficial effect exerted by EPO during experimental SAH.4–5 Thereafter, Springborg and colleagues’ reinforced our intuition and expanded the available findings on this topic to producing the first clinical trial, which, however, was inconclusive due to poor patient recruitment.6

In their study Tseng and coworkers have shown that EPO can have a chance as a neuroprotectant following aneurysmal SAH in humans. Although the study has some limitations, most of them stated by the authors (that is, small sample size, a single predefined dose of EPO, a single trial center, and lack of timed CT scan data), it demonstrates in humans what we have observed in our experimental studies. Administration of EPO has been shown to be effective in limiting cerebral vasospasm and ischemia following aneurysmal SAH.

Although the study opens a new avenue in this field, some issues deserve consideration. First, is recombinant human EPO (rHuEPO) administration safe in the sitting of SAH? It must be taken into account that all the information so far available regarding the safety of rHuEPO in humans comes from its use in treating different clinical conditions. The logical extension of these arguments is that translating such information from anemic rHuEPO-treated to SAH-affected patients can be misleading because interaction and influence between rHuEPO and different physiological variables as well as with common drugs used in SAH patients are unknown. Moreover, although rHuEPO is in general a well-tolerated drug, sev-
eral lines of evidence have shown that therapy with recombinant EPO can result in hypertension, hypertensive encephalopathy, accelerated atherosclerosis, seizures, and thrombotic/vascular events. In the present study, the authors did not observe adverse effects during the treatment. Although encouraging, these findings can be related to a short-term treatment and low-dose EPO. In this regard, in our studies we have provided evidence that rHuEPO treatment at a dose of 1000 UI/Kg, administered every 8 hours, is effective in reducing cerebral vasospasm, ischemic brain damage, and significantly capable of improving neurological outcome. The dose used in the present study is the lowest dose known to be effective following SAH. However, it can be argued that the unfavorable results from the first clinical trial and the weak findings of the present study can be related to the small dose used and the frequency of administration.

In this regard, it is well known that vasospasm and cerebral ischemia after aneurysmal SAH follow a different temporal course in humans than animal models. In preclinical studies, EPO has been considered effective at a dose starting from 400 UI to 1000 UI/kg with a duration from 24 to 72 hours. In humans, however, there is often an early, short-lived phase occurring immediately after SAH, followed by a prolonged or chronic phase. The delayed vasospasm, seen on angiography in 40–70% of patients with SAH in the 2nd week posthemorrhage, appears clinically to be most important. Consequently, there is a rationale for starting and continuing neuroprotection for up to at least 14 days after SAH onset to achieve stronger effects.

In the light of these observations, further studies must be carried out to determine the safety of EPO in the setting of this new clinical application, optimal tolerated dosages, therapeutic time window, and duration of therapy. Increased blood viscosity and possible thrombotic events seem the most reliable complications following prolonged EPO treatment. Accordingly, the new EPO-derived drugs without erythropoietic effects so far developed and shown to have good efficacy in a variety of disease models should be considered to warrant a better chance of success.

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