Sulci as landmarks

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Synopsis

When spatially normalizing images of the human cerebral cortex, the folding pattern is often used as a proxy for architecture. However, the variability of the folding pattern across individuals creates a lot of difficulties. Furthermore, the mechanisms underlying gyrification are still under exploration, and the links between folding and architecture are unclear outside primary areas. New computational methods focused on cortical sulci have been designed to support the research programs aiming at improving the role of sulci as architectural landmarks. They provide automatic recognition of the sulci, sulcus-based spatial normalization, and models of the variability of the shape of the sulci.

Keywords

Cerebral cortex, Cortical folding, spatial normalization, Folding Pattern, Variability, Sulcal Roots, Sulcal Pits,
Matching brains is a basic need in Neurosciences. Brain architecture provides the guideline for this matching, because architecture stands as the topology of the underlying neural network. Provided that the brains to be matched come from the same species, this topology is supposed to be largely invariant across standard subjects. With regard to the cortical surface, structural architecture mainly amounts to multiple overlapping parcellations defining homogeneous areas for various microstructural features (Amunts, Hawrylycz et al. 2014). Such parcellations can stem for instance from cytoarchitectony, myeloarchitectony, receptor densities or structural connectivity profiles. One of the goals of matching brains is the study of functional architecture, which is supposed to fit in a way or another structural architecture.

In neuroimaging, matching brains is usually understood as spatially normalizing images of these brains. Each brain is warped toward a so called standard space in which the localization of architectural modules is supposed to be stable across subjects. Unfortunately, the T1-weighted MR scans classically used to perform this spatial normalization include very few architectural features relative to the cerebral cortex. The main information included in these scans is cortical thickness and the morphology of cortical folds. Since the link between the cortical folding pattern and architecture is unclear except in primary areas (Welker 1988), the earliest spatial normalization techniques did not strongly focus on aligning cortical sulci. This situation resulted also from the difficulties raised by the large variability of the folding pattern across individuals. The template brains driving the warping to the standard space were fuzzy brain images obtained by averaging a large number of normalized brain images without sulcus alignment. Hence, architectural compliance of spatial normalization was poor at the onset of the field of neuroimaging.

During the last years, however, impressive advances have been achieved by spatial normalization technology with regard to sulcus alignment. While our understanding of the architectural value of sulci is still weak, it did make sense to use them as a proxy, as long as better architectural clues were missing. Standard approaches like Dartel in 3D (Ashburner 2007), or Freesurfer and Civet for the cortical surface (Fischl, Sereno et al. 1999) (Lyttelton, Boucher et al. 2007), are very efficient at aligning automatically
primary sulci, which was shown to improve the alignment of primary architectonic areas (Fischl, Rajendran et al. 2008). Recent advances in neuroimaging will now lead to improve further the architectural compliance of spatial normalization using multimodal data, for instance myelin maps, or diffusion-based connectivity information but also functional landmarks, that can be easier to obtain than architectural landmarks in some areas (Robinson, Jbabdi et al. 2014). But refining the use of the cortical folding pattern is still possible (Yeo, Sabuncu et al. 2010), which is the topic of this paper.

**Defining sulci and gyri**

While a hallmark of the human brain is the circonvoluted shape of its cerebral cortex, the detailed road map of its folding pattern is rarely a topic of interest. Folding is often only considered as an evolutionary trick increasing the surface area of the cortex without impacting the skull volume. From this point of view, the detailed topography of the folding pattern is meaningless. The medicine atlases provide the nomenclature of the primary sulci that are presented as interesting landmarks to distinguish large brain modules like lobes and gyri, or to localize primary functional areas. These primary sulci are the first to develop during ontogeny. For instance the central sulcus (see Fig. 1) delimits frontal and parietal lobes and hosts respectively primary sensory and primary motor areas in its two walls. While actual modules of the brain are not sulci but gyri, morphological descriptions usually focus on sulci because they are geometrically well defined. Most gyri are delimited by two parallel sulci, but this definition fades away at the level of sulcus extremities or in case of sulcus interruption.
Surprisingly, the anatomical literature is rather sparse of rules to overcome the variability of the cortical sulci topography across individuals. This variability however is very disturbing when trying to project an atlas of the sulci onto a specific brain, which is illustrated in Fig 1, 2 and 3. Furthermore, the most comprehensive description of the variability of the folding patterns has been provided for a set of only 25 brains (Ono, Kubik et al. 1990), and many configurations have never been described. Long primary sulci can be split into pieces by annectant gyri (Regis, Mangin et al. 2005) (see Fig 6.A). These pieces can be recombined in non standard ways to create unusual folding patterns without clear link with the anatomical nomenclature. Furthermore, primary sulci are surrounded by numerous shallower folds increasing the complexity to be decrypted. While an exquisite nomenclature of these secondary and tertiary folds has been recently proposed (Petrides 2012), comprehensive studies of their variability across individuals are limited to a few areas (Zlatkina and Petrides 2010, Segal and Petrides 2012).
Figure 2: Twelve left mesial cortical surfaces processed like for Fig. 1.

Figure 3: The nomenclature used in Fig. 1 and 2.
After a careful observation of Fig 1 and 2, it becomes clear that the reliable identification of sulci is a challenge. We still miss a gold standard method providing a clear-cut consensual solution whatever the configuration. The following sections describe several strategies aiming at the emergence of such a method. They rely on various tools from computational anatomy facilitating the explicit manipulation of cortical folds. These tools support research programs aiming at testing systematically the links between the folding process and architecture, which probably differs between primary and secondary folds. Note that in spite of our current lack of understanding of these links, the variability of the geometry of the sulci is already considered as a proxy of the underlying architectural variability, which is exploited for the search for developmental biomarkers (Mangin, Jouvent et al. 2010). For instance, in epilepsy, it was shown that abnormal in utero development like dysplasia can let a signature in the folding pattern (Regis, Tamura et al. 2011). In schizophrenia, the shape of the superior temporal sulcus in the right analogue of Wernicke area predicts hallucination phenomenology (Plaze, Paillère-Martinot et al. 2011). In preschoolers, the folding pattern of the midcingulate cortex influences cognitive control abilities (Borst, Cachia et al. 2014).

Explicit sulcal constraints in spatial normalization

At the time where standard spatial normalization was not satisfying in terms of gyral matching, some teams have developed alternative techniques explicitly aligning primary sulci drawn manually on 3D rendering of the brains (Thompson and Toga 1996). Whatever the progresses achieved by modern normalization tools, imposing explicitly sulcus-based constraints is still useful to deal safely with unusual folding patterns (Van Essen 2012). Thanks to dedicated computer vision approaches, it is now possible to define automatically more than 120 cortical sulci (Perrot, Rivière et al. 2011) in order to provide them to a sulcus-based normalization framework (Auzias, Colliot et al. 2011) (See Fig. 4). The automatic recognition process is not error prone and can be questioned, but once the folds have been extracted using a computational technique (Mangin, Frouin et al. 1995), they can be matched manually to any nomenclature of sulci in a reasonable time, according to the needs. Now that such a versatile framework has been designed, the open issue is: what are the sulci to be aligned across brains?
Figure 4: Sulcus-driven 3D spatial normalization.

A: Iterative refinement of a group-based sulcal template aligning individual simplified sulcal imprint. B: Detailed illustration in the central sulcus area using 5 individuals and 3 alternative alignment procedures. Note that explicit sulcal constraints prevent mismatch. C: Group-level activation maps obtained in the left hemisphere for extension of the right wrist for DARTEL (Ashburner 2007) and DISCO (Auzias, Colliot et al. 2011). Maps from 10 subjects are superimposed on the corresponding mean structural image computed for each method; t≥4.0, p≤0.0001 voxel level uncorrected (Pizzagalli, Auzias et al. 2013). Explicit sulcal constraints improve t values and activation size.

While the interest of imposing the alignment of sulci in primary areas has been proven (Fischl, Rajendran et al. 2008), the question is largely opened elsewhere. Future work will lead to assess one by one the added value of each sulcus in the normalization process, relative to its capacity at improving the alignment of architectural data like postmortem architectonic maps or in vivo fMRI maps (see Fig. 4). In a context where the amount of information planned to be used for normalization is rapidly increasing, it would be important to discard the sulci generating misleading constraints. A seminal work in this direction has been achieved using machine learning techniques to tune the influence of the different folds in the context of surface-based normalization (Yeo, Sabuncu et al. 2010).
In non primary areas, the number of studies reporting strong links between folding pattern and functional maps is very low (Watson, Myers et al. 1993, Amiez, Kostopoulos et al. 2006). Interestingly, one recent study reports such links in the fusiform area not only with functional maps but also with postmortem cytoarchitectonic maps (Weiner, Golarai et al. 2014). In our opinion, this global lack of knowledge reveals the difficulty of this kind of investigations more than the absence of link. The variability of the folding patterns in non primary areas coupled with the difficult inference of individual activation maps are a huge impediment. Advanced dedicated software will help to clarify the situation.

The fact that a lot of architectonic transitions are not marked by a fold has sometime been raised to advocate for a poor architectural value of the folding pattern (Roland, Geyer et al. 1997). But none of the architectural hypotheses about the causes of the folding imposes a one to one systematic relationship (Zilles, Palomero-Gallagher et al. 2013). For instance, the idea that a protomap of the primary sulco-gyral organization with architectural flavor may exists in the outer subventricular zone (Reillo, de Juan Romero et al. 2011) or in the subplate (Kostovic and Rakic 1990) of developing gyrencephalic brains would not forbid further architectonic differentiation to occur inside primary gyri. Another disturbing observation is the fact that the bottom of some folds does not correspond to any architectonic borderline (Roland, Geyer et al. 1997). But such folds could provide clues about other levels of architectural segregations, related for instance to connectivity profiles (Welker 1988). The tension-based hypothesis, which assumes that mechanical properties of the fiber tracts is one of the causes of the folding process, would support this idea (Van Essen 1997). In front of the complexity of the phenomena driving the cortical folding process, a pragmatic approach seems mandatory. Comparing sulcus-based normalizations using different subsets of sulci could help deciphering the contribution of each causal hypothesis to the folding dynamics.

Patterns and Manifolds

Forcing the alignment of a sulcus across a group of subjects raises a lot of issues. For instance, it is unclear whether the putative associated architectural landmarks are related only to the bottom of the sulcus or also to the top of the walls of the sulci, or
even to the top of the delimited gyri. Furthermore, as illustrated in Fig. 1 and 2, a sulcus can have very different patterns across brains. These patterns are related for instance to variable interruptions or branches (Ochiai, Grimault et al. 2004). In the normalization approach described in Fig. 4, branches are automatically pruned out, and the constraint acts only on the sulcus bottom and top lines. Nevertheless, because of interruptions, the point to point alignment between two sulcus bottoms is an ill-posed problem that is currently overcome through regularization of the deformation field: the warping between the two sulci has to be very smooth and cannot afford aligning perfectly all the details of the sulcus shapes (Auzias, Colliot et al. 2011). When a sulcus is interrupted by an annexant gyrus (see Fig. 6.A), the two sulcus pieces often appear as two parallel sulci at the level of the interruption. During development, the folding process acts independently for each piece which leads to elongation without match in continuous sulci. The regularization of the warping deformation prevents the spurious alignment of these supplementary parts. Similarly, manual approaches to the definition of sulcal constraints impose smooth continuous drawing at the level of interruptions (Thompson and Toga 1996).

Nevertheless, understanding the potential architectural value of the different sulcus patterns is of key interest for improving normalization. The regularization strategy mentioned above has few chances to be optimal in terms of architecture alignment. Hence we have to learn explicitly how to match different patterns to be compliant with architecture. For this purpose, the recent success of multi-template based segmentation methods is suggesting a two level strategy. This success shows that registration techniques provide more meaningful alignment when dealing with similar patterns. Hence, for each sulcus, normalization should be applied independently in subgroups of subjects with the same sulcus pattern, leading to several independent standard spaces. Performing independent group analysis of functional or architectonic maps in each of this space would lead to pattern-specific architectural maps, as illustrated by the seminal work on the fusiform gyrus (Weiner, Golarai et al. 2014). Finally, a second stage of meta-alignment informed by architecture can be developed to bridge the gap between these pattern-specific standard spaces. Note that this meta-alignment stage may have to give up on using the usual diffeomorphism framework whenever different morphological patterns reveal non compatible spatial embedding of the underlying architecture.
Figure 5: Pattern-specific templates.

Isomap manifold learning algorithm captures a one dimensional approximation of the high dimensional space spanned by the central sulcus. Moving averages of the sulcus morphology or of registered individual fMRI maps can be computed along this manifold to get pattern-specific templates (Sun, Pinel et al. 2012). Here, using 252 subjects, the position of the “putative hand knob” in the pattern-specific template moves dorsally from one side to the other side of the axis, while a second lower knob appears. The corresponding motor activation template follows the hand knob, confirming that this well-known functional landmark holds even for extreme configurations. A reading activation template extends toward premotor areas while the second knob appears, which could provide clues about the architectural value of this second landmark.
Applying this strategy requires the definition of patterns in the spirit of what was done for 25 brains in the atlas of Ono (Ono, Kubik et al. 1990). Automatic data mining techniques have been designed to extend the work of Ono to larger datasets in order to obtain a reliable estimation of frequent sulcal patterns (Sun, Perrot et al. 2009, Coulon, Fonov et al. 2012). Applying non supervised clustering to thousand of brains, they aim at providing an exhaustive dictionary of templates of sulcal patterns to be used when designing the multi-template normalization strategy mentioned above. Several complex issues have to be addressed. First, what should be the optimal scale for these local templates of patterns? Ambiguities in sulcus recognition lead to split the global folding pattern into groups of sulci minimizing intergroup mismatch rather than dealing with sulci one by one. Second, once local templates of patterns and architecturally compliant alignments between them have been defined, how to build a global standard space?

The concept of sulcal pattern is relatively easy to understand: for instance, the central sulcus exists either as one single continuous furrow, or as a split furrow in case of interruption at the level of the middle fronto-parietal pli de passage (Regis, Mangin et al. 2005). In practice, clustering techniques are challenged because of the existence of continuous variations from one pattern to another. With regard to the central sulcus interruption, for instance, the pli de passage can be more or less buried, leading to a shape continuum between the interrupted configuration and the configuration with a very deep pli de passage. Hence, defining the optimal number of patterns is difficult. As an alternative, it was proposed to capture a low dimensional manifold approximation of the high dimensional space spanned by each sulcus (Sun, Klöppel et al. 2012), using Isomap algorithm, a modern version of MultiDimensional Scaling (Tenenbaum, de Silva et al. 2000). The multi-template based strategy mentioned above has been directly extended to this manifold strategy as illustrated in Figure 5 (Sun, Pinel et al. 2012). The manifold approach refines the multi-template strategy because it provides the transmutation of the architectural templates along with the transmutation of morphological patterns, which is a guideline for the second level alignment.
Figure 6: Sulcal roots and sulcal pits.

A: Qualitative maps of the “plis de passage” or annectant gyri leading to propose the concept of sulcal roots, the atoms of the folding pattern supposed to stem from ontogeny (Régis 1994). B: a map of the lateral sulcal roots for a brain oriented according to Talairach space (Regis, Mangin et al. 2005). C: a group map of sulcal pits, the deepest points of the folding pattern in adults (Im, Jo et al. 2010). D: a group map of sulcal pits in one year old infants (Meng, Li et al. 2014).

Sulcal Roots and Sulcal Pits

Primary sulcus interruption is a major difficulty for spatial normalization whatever the strategy. The unusual fold recombinations resulting from these interruptions can puzzle the best experts of cortical morphology. These interruptions result from the
unusual development of annectant gyri usually buried in the depth of the sulci. Mapping these gyri often called “pli de passage” (see Fig. 6A) leads to question the scale chosen by the first anatomists who coined the sulcal nomenclature. Looking for an alphabet to perform a syntactic analysis of the variability of the folding patterns led to propose the concept of “sulcal roots”, indivisible atomic folding entities supposed to be stable across subjects (Régis 1994, Regis, Mangin et al. 2005). Sulcal roots are supposed to emerge as the primal sketch of the sulci during development. Qualitative maps of sulcal roots were proposed as a synthesis of embryology and “pli de passage” maps (see Fig. 6B).

Recent works on the geometry of the cortical surface have put forward a sibling concept called “sulcal pits”, namely the deepest points of the folding pattern (Lohmann, von Cramon et al. 2008, Im, Jo et al. 2010) (see Fig. 6C). Sulcal pit maps and sulcal root maps are highly similar, which is not surprising. Note however that we do not know enough about the folding process to guarantee that the deepest points are stationary on the cortical surface during development. For instance, they could slide along the sulcus bottom. Hence, emerging studies with premature babies and infants are of high interest (Lefèvre, Leroy et al. 2009, Operto, Auzias et al. 2012, Meng, Li et al. 2014)

These mind opening concepts provide new ways to explore the links between morphology and architecture. For instance, sulcal root and sulcal pit maps reveal striking alignments with the global geometry of the cerebral cortex. This led to design dedicated coordinate systems mimicking latitude and longitude on earth (Toro and Burnod 2003, Clouchoux, Rivière et al. 2010, Auzias, Lefèvre et al. 2013) (see Fig. 7). The meridians and parallels underlying these systems can be observed in the cortex of a lot of mammals (Welker 1988), and are supposed to stem from phylogeny and ontogeny. They could even have an analog in white matter organization (Wedeen, Rosene et al. 2012). Hence they could have a strong architectural content.

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Figure 7: Meridians and parallels
Top row: extracting sulcal bottom lines using Morphologist pipeline of BrainVISA.
Middle row left: model of cortical sulci organization in meridians and parallels; center: general principle of the HipHop method (Auzias, Lefèvre et al. 2013); right: a cortical surface with sulcal lines, flat harmonic mapping $f$ of the same surface (sulcal lines and mean curvature of the original surface), result of the registration with the model (mapping $g$), resulting coordinate system. Bottom row: sulcal lines of 62 subjects in the rectangular domain after harmonic mapping $f$; same after registration with the model; same on the average surface of the 62 subjects.
References


