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INDIVIDUALIZED SULCAL AND GYRAL CORTICAL ANATOMY: A NEGLECTED CONCEPT?

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Future unavoidable development of individualized brain anatomy as a part of personalized medicine requires large databases from a vast number of individual brains. The simple descriptions, important in the clinic, demonstrated the wide morphological and morphometric variability of the sulci and gyri. Today, it is no longer enough, like in traditional anatomy, to simply describe one single, several, or even "all" sulcal/gyral variations in one region of the brain. Potential problems in the comprehensive analysis of their patterns with attempts to suggest further research are briefly reviewed. The medial hemispheric surface is suitable for a morphological pilot study of complete sulcal and gyral variability. Sulcal patterns should be presented in simplified linear form rather than as detailed images, and one useful simplification for analyzing gyral patterns, the essential gyral line, is described. Simultaneous investigation of gyri and sulci is recommended, but the problem is combinations of specific patterns in different percentages. Sophisticated algorithms could recognize cortical patterns and calculate their possible combinations. Anatomical terminology is an unavoidable component of these studies. Big data about variations of sulci and gyri would be useful in personalized medicine but also in genetic studies of potential laws and inheritance of their associations.
Key words: Human brain, sulci, gyri, shapes, variability, analysis

INDIVIDUALIZOVANA ANATOMIJA KORTIKALNIH ŽLEBOVA I VIJUGA: ZANEMAREN KONCEPT?

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Predstojeći neizbežan razvoj individualizovane anatomije mozga, kao dela personalizovane medicine, zahteva velike baze podataka sa ogromnog broja pojedinačnih mozgova. Jednostavni opisi, važni za kliniku, pokazali su široku morfološku i morfometrijsku varijabilnost žlebova i vijuga kore mozga. Međutim, danas više nije dovoljno, kao u tradicionalnoj anatomiji, da se samo jednostavno opiše jedna, nekoliko ili čak „sve" varijacije žlebova i vijuga u jednom regionu mozga. Zato su ovde su ukratko prikazani mogući problemi u sveobuhvatnoj analizi njihovih oblika, uz pokušaje ukazivanja na dalja istraživanja. Medijalna površina hemisfere je pogodna za pilot studiju sveobuhvatne varijabilnosti žlebova i vijuga. Žlebovi bi trebalo da se prikazuju u pojednostavljenom linearnom obliku pre nego kao detaljne slike, a opisana je i korisna pojednostavljena metoda analize šara vijuga, „the essential gyral line". Preporučuje se istovremeno istraživanje žlebova i vijuga, pri čemu problem predstavljaju kombinacije specifičnih obrazaca koji su prisutni u različitim procentima. Sofisticirani algoritmi bi mogli da prepoznaju kortikalne obrasce i da izračunaju njihove moguće kombinacije. Anatomska terminologija je neizbežna komponenta ovakvih istraživanja. „Veliki podaci" (big data) o varijacijama žlebova i vijuga bili bi korisni u personalizovanoj medicini, ali takođe i u genetskim studijama potencijalnih pravila i mogućih zakona nasleđivanja njihovih udruženosti.
Ključne reči: Mozak čoveka, žlebovi, vijuge, oblici, varijabilnost, analiza

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INTRODUCTION

It is now widely believed that the underlying heterogeneity of many disease processes suggests that strategies for treating an individual with a disease, and possibly monitoring or preventing that disease, must be tailored or 'personalized' to that individual's unique biochemical, physiological, environmental exposure, and behavioral profile [1]. Each human brain imagined or studied by different methods is by itself individualized. This short review uses the term "individualized anatomy," understanding that it can only be a part of personalized medicine.

Numerous descriptions of the human brain's sulcal and gyral variability are available [2] and are constantly being renewed. Although brain structure and brain function are not strictly dependent on each other, studies show that they are closely related, and the knowledge of this relationship allows the surgeon to plan procedures [3]. It is enough to mention here only two illustrative examples of the excellent and detailed traditional anatomical studies, describing a large number of variations of the occipital [4], subparietal, and parietooccipital sulci [5], as well as a monograph about anatomical variability and terminology of sulci [6]. Analysis of sulcal and gyral morphology and quantitative data is necessary also for studies of cortical development, cortical plasticity, pathological changes, comparative neuroanatomy, and the evolution of the cortex [2].

Despite the vast amount of information about the cerebral sulci, and particularly their variability [7], it is not entirely clear, apart from simple descriptions and morphometry, how to additionally treat and exploit obtained data. One of the goals could be to achieve the optimal use of these qualitative and quantitative data in different research and to explore possible genetic backgrounds or regularities of brain variability. In the available literature there is no data on whether or how often comprehensive morphological studies of all sulci and/or gyri in large samples of human brains have been reported. When sex, age, or brain side data are included, an enormous number of possible combinations of variations appear in the analysis of the individualized whole brain cortical patterns. The consequent increase in the scope of detailed research of the very large number of samples required makes work difficult, but it may be solved using artificial intelligence.

How to assess whether two sulcal/gyral shapes are similar or not, and what is the confidence limit for determining similarity? The recognition, definition, manual labeling, and typification of the sulcal/gyral shapes require training of a human observer to be able to identify sulci and gyri in individual brains. Since it is often based on the personal judgment of one or several investigators and is obviously up to the researcher (subjective error), the results of such studies are only roughly comparable. If, in order to facilitate work, the pre-labeled templates for identifying anatomical variations are used, this does not lead to an improvement of the study. The "standardization", such as the use of the intercommissural line system, also limits the accuracy of findings and can provide an illusory feeling of excessive confidence. On the other hand, these can be considered primitive, but the widely available methods still have their purpose.

During the studies of the human corpus callosum, authors more than thirty years ago encountered the problem of variable shape analysis, even if callosal shape is simpler and well delineated compared with sulcal and gyral patterns [8]. It seemed impossible to determine which callosal shapes are identical or are only similar, especially if analysis required further parcellation into callosal parts, which are without defined boundaries. Compared to this, the analysis of gyral and sulcal patterns appears several times more complex. The traditional partial descriptions with percentages reported of the morphological variations of the certain sulci and gyri, although adequate for the clinical purposes (see refs. [4, 5]), are no longer sufficient. Recently anatomical data preparation requires different new approaches for the analysis of a lot of brains to acquire actual "big data" about variable cortical morphology. Sophisticated programs or algorithms, such as artificial intelligence (the details of which are beyond the knowledge of anatomists), are needed to recognize morphological patterns and their similarities and, in some research, to apply the analysis of the fractal structure. Namely, the brain science will become more reliant on big data to provide a wealth of knowledge and can also be used to build computational models, and a model of the human brain as a "reference brain" provides important biological details [9].

This paper reviews briefly some challenging issues based in large part on the experience of the author's morphological research of the human brain cortical folding patterns, that is, sulcal/gyral shapes. To illustrate common issues in morphological studies of the cortical sulci and gyri, first are presented comparative views of photos and simplified linear presentations of sulci as examples for

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their potential use in complex analysis, which is much more than simple description. Thereafter are presented two examples of gyral variability, all based on the author's own research and experience.

Sulci

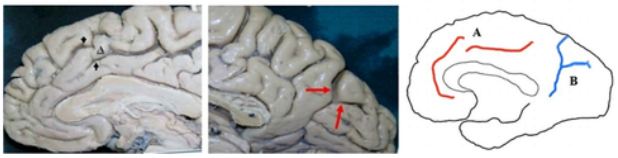

Figure 1. Left: Photo of Sulcus cinguli (17.9%) with a gyrus interposed (A). From [10]. Middle: Photo of Y-shaped sulcus parietooccipitalis - arrows (38.1%). From [11]. Right are their simplified linear presentations: A - Sulcus cinguli (red); B - Y-shaped sulcus parietooccipitalis (blue)

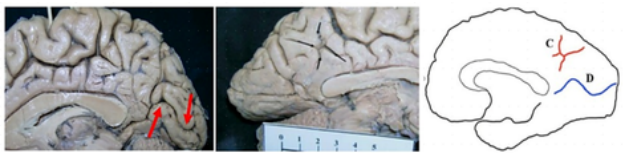

Figure 2. Left: Photo of Sulcus calcarinus - continuous, with two or more waves (36.9%) (arrows). From [11]. Middle: Sulcus subparietalis of H shape (arrows) (57.1%); from [10]. Right are their simplified linear presentations: C - Sulcus subparietalis of H shape, D - Sulcus calcarinus, with two or more waves.

There is a dilemma whether in pattern analysis the simplified linear presentations of sulci, the whole sulcal pattern of the related brain, or the whole brain imaging should be used, with a lot of details confusing or blurring the results. The answer to this dilemma of comparing “reality” or linear presentations could be the statement that the term “sulcus” is typically described qualitatively rather than as a concept or notion as a quantitative anatomical object [7]. Technically, inclusion of secondary and tertiary sulci in the linear presentations of sulcal patterns can be realized easily using different line thicknesses for showing them.

Gyri

Similar issues, as for morphological studies of sulci, can be considered for most of the brain gyri.

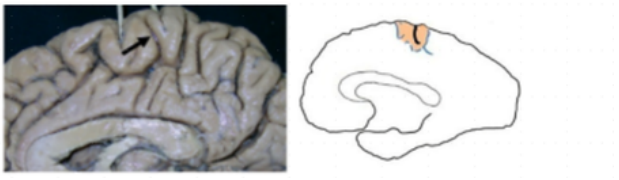

Figure 3. Left: Very rare segmented type of lobulus paracentralis, black arrow (4.8%). From [12]. Right: simplified presentation of segmented lobulus paracentralis (thick black line - the rare sulcus dividing lobulus paracentralis).

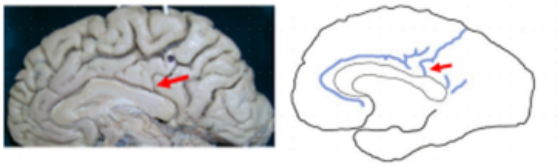

Figure 4. Left: Segmented gyrus cinguli (35.7%) divided by deep sulcus (red arrow). From [13]. Right: simplified presentation of segmented gyrus cinguli (red arrow).

Quantitative sulcal/gyral shape analysis

We do not know for sure whether the differences in the sizes of the corresponding cortical sulci/gyri really play any, perhaps even essential, role in this determination of shape similarities. When comparing the large and small structures, both of identical shapes, could these be characterized as „similar“, as the same, or not? Are these functionally absolutely "analogous" in some way, or are they functionally different either with or without certain adjustments or corrections? Related to this, for estimation of some anatomical variability and sizes, the morphometry should be used, considering it is complex. One must be careful with ambition to define everything or to measure whatever can be easily measured because it is necessary to avoid the generation of fictional numbers, which are in the realm of guesswork and are surrounded by controversy [14]. In the quantitative morphological investigations that are comparative, all material must be treated in an identical fashion, or if not, the application of corrective factors, such as for brain volume, body weight, body height, sex, age, etc., is necessary. When measuring formalin-fixed parts of the brain, the obtained sizes are not the same as on living (imaging) or fresh cadaveric brains. For example, the average volume of the orbitofrontal region after fixation by 10% formalin (3.7% formaldehyde) was increased by 5.7%, which was a highly significant change ($p < 0.01$), but the linear change of the same

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region was only 1.7% [15].
Morphometry, as almost unavoidable in sulcal/gyral research, is important for the solution of scientific problems concerning function, development, comparison, and pathological changes. It mainly includes measurements of volume, surfaces, and length of lines [16]. One systematic review [7] concluded that surface-based morphometry techniques have been shown to be particularly useful, as they allowed the description of parameters that characterize specific aspects of the cortex, such as its thickness, gyrification index, and sulcal width and depth [17]. New approaches to sulcus quantification, besides these parameters, include new ones, namely, sulcal volume, wall skewness, and the number of white matter basins [7]. However, there is a need for much more information to get out of the realm of fictional numbers we may be left in [14]. One difficulty in quantitative sulcal/gyral shape analysis, including asymmetries, is precisely establishing and defining reference points and lines with the often-unclear boundaries of the sulci/gyri being measured. Generally, main sulci are always defined, but in some studies it was necessary to use lines extending in the direction of certain sulci as the approximate boundaries of some gyri [12, 13, 18]. The problem of using inadequate methods can be potentially overcome since track tracing, imaging, and dissection are based on different biological or physical principles, and it is natural for their results to sometimes be different, but they are often complementary [19].

In the quantitative studies of the gyrencephalic cortex, additional difficulty is morphological complexity, related to its convoluted structure. One of the ways to solve this was the use of fractals. Fractal dimension has been widely used to provide a quantitative description of structural cortical complexity; it summarizes the morphological detail of an object in a range of spatial scales and was positively associated with the folding area in both hemispheres [17, 20]. Namely, one of the most salient properties of the brain's macroscale geometry is gyrification, the fractal-like folding of the cerebral cortex [21]. The fractional dimensionality of gray matter (cortical complexity) can be more sensitive to age-related differences than other metrics of cortical integrity, and fractal analysis has been applied to anatomic/histological images and neuroimaging for quantifying the developmental complexity of the human cerebral cortex [22, 23].

The essential gyral line (EGL)

The increase of the cortical volume in larger species is almost entirely due to a disproportionate expansion of the cortical surface area, and the brains change their shape by becoming folded as they increase in size [24, 25]. The human cortex develops a complex structure by increasing the frequency of folds and the convolution of gyral shape, rather than by deepening sulcal regions [20]. The length of the interconnected fibers reduced by folding the cortical surface shortens the radial and tangential distances between brain regions [25]. Recognition of gyral patterns does not have the same meaning as recognition of sulcal shapes. One reason for this is gyro-sulcal functional difference in cognitive performances, because gyral regions as well as intergyral connections consistently participate more as functional information exchange hubs than sulcal ones, contributing to accurate mapping between brain anatomy and function [26]. An additional reason is the well-known sulcal-gyral difference, where the thickness is larger at ridges (gyri) than at valleys (sulci) [27].
In spite of the specific architecture of the cerebral gyrus inner core [19], generally an increase in the relative number of gyri can only be achieved by reducing the gyral width, which predicts an upper limit to cortical folding [28]. Related to this, the concept of the "gyral window" represents the region through which fibers must pass when leaving or entering the gyrus [28]. To this gyral window corresponds "the essential gyral line" (EGL) as its projection on the crown of the gyrus, which showed as suitable for indicating the basic direction of the gyrus (Fig. 5) [29, 30, 31].

Figure 5. The essential gyral line (EGL—interrupted line) indicates (projects) the longitudinal direction of the gyral window (part of it indicated by square). According to [28, 29, 30, 31].

Several following facts support the use of the EGL. The inner cortical surfaces presenting gyral white matter for observing folding patterns [20] correspond both to the

gyral window and to the EGL. After removing the cortex, the exposed gyral subcortical white matter takes the form of ridges that reproduce the gyral anatomy [19]. The EGL also corresponds to the definition of the gyral white matter crest line on the cortical surface, which, used in sulcus construction, also defines the gyrus [7]. Crest lines, as a powerful tool in medical imaging, follow the convolutions of the cerebral sulci and gyri. These lines should satisfy the criteria of position, continuity, and uniqueness, have a nice mathematical background, and be feasible to identify automatically [32]. The calculation of the projection of the gyrus midline can be performed by imaging, and some sulcal and gyral constructions can be automated by existing methods and public tools [7]. More gray matter is present on the surface (gyri) than in the depth (sulci) of the cortex, because the gyri are universally thicker than the sulci [27], which also favors the applicability of EGL.

The findings of more frequent sulcal than gyral asymmetries, with the differences in the frequency of asymmetries depending on the method (simple observation vs. the EGL), could be of importance for research of cortical asymmetries [29, 30]. This finding that morphological asymmetries of gyri were significantly "reduced" by use of EGL suggests that in such analyses the shape of gyri, rather than sulci, may be fundamental.

Adult human brain and sulcal/gyral invariability

While the morphology of human primary and secondary sulci/gyri is practically unchanging during healthy adult life, this is not yet entirely certain for so-called tertiary sulci/gyri. Related to this could be the findings of more pronounced sulcal asymmetries on the level of tertiary sulci and that the individual sulcal variability may be related to very large coefficients of variation of total length of tertiary sulci [31]. It opens the question: are tertiary sulci somehow related to specific cytoarchitectonic subfields ("campuli"), or do they represent their boundaries? The extremely nonuniform aging of the brain among the various brain regions [33] can also be related to specific cytoarchitectonic subfields. Could there be a possible role of adult brain plasticity at the meso- or microscale levels since it was shown [34] that an environment's features strongly shape the quality and nature of the functional representations formed? Recently it is impossible to exclude that some long-term functional processes, by long-lasting dynamics, affect not only adult brain functioning but also its morphology on micro- or mesoscales. In spite of the very limited capacity of the adult brain to form new connections after stroke, studies indicate that post-stroke axonal sprouting occurs in mice, rats, primates, and humans (see [35]). The changes in neuronal sizes and collateral axonal sprouting, as well as in non-neuronal components (glia, capillaries, vasculature, and even the liquor bulk flow), will also impact MRI signals and must all be accounted for [36, 37]. The brain, once considered to be a fixed and stable organ, is now viewed as dynamic, flexible, and adaptive, with documented neuroplastic structural changes in healthy human brains as a result of normal processes that occur with learning (see [36, 37]). Given the microscopic nature of training-dependent structural changes in animals and the relatively low spatial resolution of MRI, it is unclear that in the human adult brain these changes can be reliably detected [38]. The current neuroimaging techniques cannot directly inform us about the underlying cellular events mediating the observed effects, and phenomena visible via MRI are likely never the result of a single process happening independently [36].

Broader aspects of individualized brain anatomy

Imaging can also be some kind of „identification method" of distinct patterns for each individual brain, like fingerprints. The research of brain sulcal/gyral variability is of clinical significance, because anatomical knowledge of their shapes is important for neurosurgical procedures and diagnostics, but this knowledge is not sufficient: brain function should be studied at the individual level to optimize the results of cerebral surgery [3]. Recently, nothing is known about potential associations of variable sulci on a single brain, especially if they occur in different percentages. Generally, we don't know if there is a need to establish rules for predicting and identifying potential combinations of associated different variable sulci/gyri on an individual brain in a large population (e.g., associations of sulci A, B, C, and D from Figs. 2 and 3) based on the data obtained. The occurrence of the very different sulcal percentages excludes simple mathematical combinatorics, correlations, and predictions, but its determination is possible with the help of imaging methods and of artificial intelligence. So obtained results could be useful in other research for easier and more accurate identification of cortical regions on each individual brain.

However, each of the numerous anatomical variations of the human brain surface should be accounted for in many other studies, complicating the generalizations of other anatomical data (e.g., about vascularization, receptorarchitectonics, cytoarchitectonics, connectomics, and neuropsychology), as well as for analysis of potential genetic influences. If connectome analysis is applied to the gyri, an additional problem due to their variability is defining the location of origin and/or end of the tracts. Variation in the brain's gyrification pattern must be considered as a factor that may impact the understanding of short-range connections and which prevents conclusions from being drawn from isolated cases and imposes the study of many subjects [19]. Besides limitations related to the methods or to morphological variability, new data about frontal lobe short association fibers obtained by various imaging methods generally complement the anatomical data [39].

The brain morphology in the sagittal plane is significant because it is the only definitive and inherently uniform, whatever the morphological type of the brain [40], and the mediosagittal plane is one of the key anatomical landmarks in the human brain [41]. Therefore, it could be of interest to start the wide individualized brain research with a detailed but completed anatomical sulcal/gyral analysis of the medial hemispheric side, which is practically in the mediosagittal plane along the falx cerebri.

The application of modern data-intensive methods, including imaging protocols, has revealed a great deal of inter-individual variation. Much of the personalized medicine is related to the findings of genetic studies, because each individual possesses subsets of literally many millions of genetic variants [1]. Studies by different magnetic imaging to investigate genetic associations in defining intermediate phenotypes and the effects of common genetic variants have broad implications for the advancement of both anatomical and functional knowledge (see in [42]). The interindividual variation in human brain size is almost entirely determined by genes, but overall cortical gyral patterns, though significantly affected by genetic factors, are determined primarily by nongenetic (random environmental) factors [43]. Finally, some results suggest that genetic, geometric, and physical factors during brain development are closely interrelated [27]. Individual variation in anatomy affects perceptual and cognitive abilities, but it is not known whether anatomical differences existed prior to the training or environmental event [36]. Today it is generally clear that now there is a need to overcome traditional anatomy and to fully describe each individual brain, or in other words, the need for individualized brain anatomy.

Terminology issues

All considered issues have an impact on the use of adequate terminology. The corresponding terminology with the use of correct unified terms is needed, not only for the common but also for at least the more frequent variable sulci and gyri. For numerous relatively minor or rare variants, there are no suitable anatomical terms, and these variations would be difficult to name. Therefore, one should try to establish certain regularities, such as the limit up to which the frequency of the rare anatomical forms found would be used in the creation of specific terminology. However, when such terms are applied to different individual brains, it would practically make systematic descriptive classification impossible. In spite of a consensus that the inclusion of names for trivial or variably present structures should be avoided and not be included in Terminologia Anatomica, they may find their place in alternative or specific versions of anatomical terminology [44]. However, certain numerical systems of codes can be created and used, such as in Terminologia Anatomica or in Terminologia Neuroanatomica [45, 46].

Also, with the development of advanced translator programs, practically all world languages could be officially included in order to avoid any errors in medical communication [47].

CONCLUSION

Individualized human anatomy as a specific item can only exist as a part of the development of personalized medicine, which is the practice of characterizing an individual on different levels and scales (macro- and mesoscales) and where inter-individual variation will continue to be identified [1]. This short review considers potential possibilities and problems in the analysis of cortical sulcal/gyral morphology and tries to indicate some ways for further studies of its variability. It is no longer enough, like in traditional anatomy, to simply describe one single, several, or even "all" sulcal/gyral variations in only one region of the brain. Now, the variable sulcal/gyral patterns of entire individual brains in wide populations should be described. This is very complex research if, in

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data processing, combined associations of variable sulcal/gyral patterns are present in very different percentages. Simplified linear presentations of sulci can be convenient for in-depth analysis of their variability. Into one comprehensive morphological analysis, sulcal pattern should be included equally as a gyral one, in spite of the possibility that gyral morphology can be more important than morphology of sulci. The medial hemispheric surface is a suitable region for the pilot study of its complete sulcal and gyral variability. The EGL described here can be considered as suitable for the research of gyral patterns in wider use. Cortical anatomical variability overlaps with problems in research on connectomes, cytoarchitectonics, and receptorarchitectonics, where there may not be a match with variable sulci and gyri, and they themselves may be variable. It is also inevitable to resolve terminological problems during these investigations.

Consequently, in the deep research of sulcal/gyral shapes and patterns of the human brain, the enormous need arises for and justifies integrated study centered on education in the disciplines of science, technology, engineering, and mathematics (STEM) referring to integrated knowledge and skills from those fields as is defined [48]. The unavoidable approach to individualized brain anatomy may have justification only as a part of personalized medicine. The breakthroughs in all considered directions could be widely used both in the clinic and in neuroscience research.

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