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Transcranial sonography: a technique for the study of the temporal lobes of the human and non-human primate brain

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Summary

We developed a modified transcranial sonography technique to study the morphology of the temporal lobe, a brain region involved in language, memory and social functions in humans that can be visualized in correspondence of the acoustic window of the temporal squama.
Previous studies raise the possibility that a unique derived feature of *Homo sapiens* is a relatively larger temporal lobe compared to those of other hominins and apes. Such a brain reorganization might have contributed to the evolution of various "higher" cognitive functions of *Homo sapiens*, including language. Hence, the importance of further comparative analyses of the temporal region.
With the technique that we developed we were able to study the meninges, the subarachnoidal space and the cortex of the human temporal lobe. The spatial resolution and the ability to visualize structures of 200-300 μm size led us to hypothesize that the linear structures parallel to the subarachnoidal space might be referred to the neuronal layers of the cortex.
The low cost, simplicity and safety of the procedure suggest that this technique may have a significant potential in the comparative study of the primate temporal lobe.
Furthermore, the procedure described here can also be used for the study of vascularization of the meninges, in order to better understand the evolutionary relationships between the neurocranial shape and the middle meningeal vessels in living and fossil human species.

Key words

Transcranial sonography; brain imaging; primate temporal lobe; comparative neuroanatomy; human brain evolution; neurodegenerative diseases; chronic fatigue syndrome.

Introduction

Based on our background in clinical radiology, anatomy and biological anthropology, we were interested in studying the cerebral cortex of the temporal lobe because of the well-known involvement of this region in the processing of cognitive functions such as language and memory, which were possibly related to the natural selection that played a significant role in the evolution of *Homo sapiens* (Lieberman, 2011).

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Brain size increase and neurological reorganization were both important variables during the evolution of hominins ("hominins" refers to humans and their evolutionary ancestors back to the separation of the human and ape lineages; Gould, 2001). The evolution of the hominin brain has followed a mosaic pattern, at times punctuated, at other times gradual, with allometric and non-allometric brain size increases interspersed (or interdigitated) with episodes of reorganization of the brain's nuclei, fiber tracts and lobes (Holloway *et al.*, 2004). Thus natural selection has acted on brain size as a whole but also in a mosaic-type pattern on particular regions of the brain such as the temporal lobe that has undergone relative increase.

In fact, a few analyses, measuring regions of the brain with use of Magnetic Resonance Imaging (MRI), have shown that the relative size of the temporal lobe is as much as 25 percent greater in humans than in apes (Semendeferi, 2001; Rilling and Seligman, 2002; Schenker *et al.*, 2005), although this type of studies suffers from small sample sizes and the challenge of measuring lobe size accurately. Temporal expansion is probably due to a larger amount of white matter in the lateral and inferior parts of the lobe (Rilling, 2006). It is impossible so far to be definitive about the precise time frame when the temporal lobe became bigger, but several analyses show that the middle cranial fossa, which houses the temporal lobes, is about 20 percent wider and longer in *Homo sapiens* than in other species of *Homo* (Lieberman *et al.*, 2002, 2004; Bastir *et al.*, 2008; see also Maier and Nkini, 1984; Seidler *et al.*, 1997; Baba *et al.*, 2003). These analyses, as well as another more recent study (Bastir *et al.*, 2011), raise the possibility that a unique derived feature of *Homo sapiens* is a relatively large temporal lobe, possibly in those regions that are implicated in the processing of language. This expansion requires further study, and efforts to make inferences about cognitive changes from data on brain shape are tentative at best. But if correct, they raise some interesting hypotheses. The temporal lobe is associated with complex cognitive functions relevant to the organization of sensory inputs and memory, e.g., for words, images, sounds, and smells (Carter, 1999). Thus, the temporal lobes play key roles in language and other tasks that involve sensory perception and processing (Kandel *et al.*, 2000). It can be therefore hypothesized that selection for various "higher" cognitive functions, including language, helped to drive the temporal lobe increase.

With regard to this issue, of particular interest is Wernicke's posterior receptive language area in the temporal lobe. A site within this area, the planum temporale, is implicated in human communication (both spoken and gestural) and musical talent, and shows a left-hemisphere dominance. In most humans, the Sylvian fissure associated with the left planum temporale extends more posteriorly. Evidence for this asymmetry has been found in fossil endocasts in *Homo habilis*, *Homo erectus* and *Homo neanderthalensis* (Holloway, 1980). More importantly, an asymmetrical planum temporale pattern has also been demonstrated in chimpanzees (Gannon *et al.*, 1998; Hopkins *et al.*, 1998). The most probable explanation of this presence in great apes is that the common ancestor of these and humans had asymmetrical centers that were involved in communication, and that these structures underwent independent evolutionary modifications in chimpanzees and hominins. In fact, comparative neuroanatomy studies have identified more subtle differences in sub-organization (that is, "microanatomy") that seem to be unique to human brains. It has been found that the dimensions of the vertical columns of neurons in the neocortex, known as "minicolumns", differ between humans and chimpanzees in the planum temporale (Buxhoeveden *et al.*, 2001; Buxhoeveden

and Casanova, 2002). These columns turn out to be bigger, more complexly arranged, and with more neuropil in the human planum temporale than in that of chimpanzees. In addition, it can be hypothesized that there are many important differences between humans and apes in deeper parts of the neocortex. Further studies between humans and chimpanzees are thus required to investigate these differences more definitively.

Also the meningeal vascular system can be a useful tool in understanding brain evolution within hominins over the past three million years (Saban, 1982, 1984, 1993, 1995). As with cranial capacity and brain shape, the features associated with dural vasculature have been modified over the course of human evolution. In fact, the dura mater is supplied with blood vessels, known as meningeal vessels, which frequently leave imprints on the internal table of bone of the neurocranium and those imprints of the meningeal vessels make it possible to analyze vascularization in fossil specimens.

Compared with extinct human species, the most patent peculiarity of the modern human endocranial vascular system is the development of the middle meningeal vessels, covering the parieto-temporal region and a portion of the anterior occipital region. In general, there has been an increase in the complexity of the branching pattern of the anterior ramus of the middle meningeal vessels. Conversely, there has been a general reduction in the complexity of the branching pattern of the posterior ramus of these same vessels (Grimaud-Hervé, 1997). This was possibly due to an increase in cranial capacity and an alteration in the overall shape of the endocranium (Grimaud-Hervé, 2004).

Furthermore, the association between changes over the course the human evolution in the cortical anatomy and vascular organization raises questions about the actual physiological meaning of these features, in particular when considering the origin of the modern human brain. Metabolism and thermoregulation may be relevant factors in influencing morphological adaptations between brain and vessels. It is largely debated whether or not humans, having the most energy-expensive brain, also have a selective brain cooling mechanism (Brengelmann, 1993; Cabanac, 1993). Moreover, taking into account some anatomical differences in the morphology of the venous sinuses (or rather, in the traces left on the endocranial wall by the venous sinuses) among fossil hominins, this issue has been introduced in paleoneurology (Falk, 1990), the thermoregulation function being definitely relevant for brain physiology and evolution. However, despite the relevance of this topic, few advances have been proposed in this direction, with these characters being only marginally related to clear physiological processes.

Little information is also available on the modern anatomical variation of the middle meningeal vessels, on their developmental origin, on the phylogenetic homology among non-human primates, and even on their exact physiological roles (Bruner and Sherkat, 2008; Bruner *et al.*, 2011). We therefore need to provide more information on the biology and variation of the endocranial vascular systems, in order to better understand evolutionary relationships between the neurocranial shape and the middle meningeal vessels in living and fossil human species.

In summary, one of the major challenges to present comparative neuroanatomy is to identify relative differences in the size, cellular composition, detailed cytological architecture and/or connectivity of human and great ape brain areas. In fact, there are clues that human capacities are more a product of quantitative changes in specialized areas than of neuroanatomical "novelties" (Preuss *et al.*, 1999; Buxhoeveden

et al., 2001; Semendeferi *et al.*, 2001; Buxhoeveden and Casanova, 2002; Sherwood *et al.*, 2003). Therefore, in order to make easier the analyses of the meningeal and cortical structures of the human and non-human primate temporal lobes, we modified the conventional procedure for transcranial sonography using a linear probe that is normally used for muscle-skeletal ultrasound imaging. We observed that such a procedure allowed detailed visualization of the meninges and the cortex of the temporal lobe and might prove useful in evolutionary studies as well as in clinical medicine.

Materials and Methods

The ultrasounds used for imaging, also known as sub-thermal ultrasounds, are considered inherently safe and have been used for foetal imaging in utero, and virtually every part of the body, including brains of newborn babies through fontanelles. For transcranial sonography we used an Esaote MyLabFive ultrasound imaging machine approved for many applications including cephalic (brain) imaging. We used the default settings for adult transcranial imaging, but instead of a conventional transcranial probe, we used a linear probe for muscle-skeletal examination, and we selected 7.5 MHz frequency. Acoustic power was set to 1.0. The length of the probe is about 4 cm, i.e. much less than the size of the temporal cortex that we examined that is 7-8 cm. The depth of the focus was varied according the localization of the anatomical structures to be studied and gain was set accordingly between 51 and 64%. In the study of the cortex and the meninges, the enlargement (zoom) function of the ultrasound imaging machine was applied as indicated in the figures.

The procedure was performed at the Department of Human Anatomy, Histology and Forensic Medicine of the University of Firenze, Italy. The healthy volunteer subjects, all of them among the Authors of this study, gave their informed consent and the sonography was performed by a certified clinical radiologist (M.R.). Subjects to be examined laid on the conventional examination bed that is routinely used for clinical sonography with their heads on an appositely placed pillow. The probe was placed on the right temporal region in correspondence of the acoustic window of the temporal squama. Detailed knowledge of human anatomy was instrumental in correctly positioning the probe in correspondence of the temporal lobe as well as in performing voluntary contraction of the temporalis muscle (Fig. 2).

Results

During 10 min transcranial sonography, no discomfort or any type of side effect was reported by the volunteer subjects. The parameters adopted for visualization of the temporal cortex allowed to distinguish the skin and the subcutaneous tissue, the temporalis muscle, the temporal squama, the meninges and the cortex (Fig. 1). The squama of the temporal bone appeared as an hyper-echogenic (white) irregular line of about 1.5 mm thickness. It is worth noticing that the temporal squama reflected most of the ultrasounds as it is expected to occur with bone structures. However, the fraction of ultrasounds that could penetrate further in depth was sufficient to allow visualization of the meninges and the cortex.

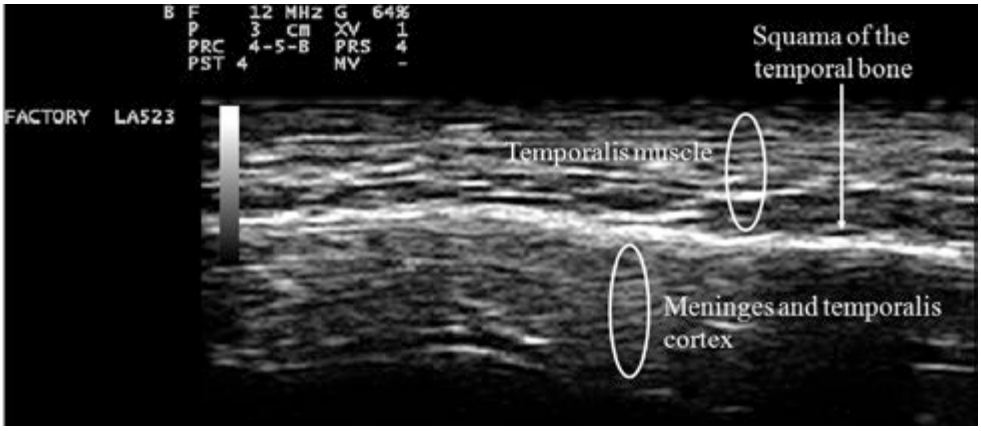

Figure 1 - Two dimension image of the temporal region obtained by transcranial sonography. Subject: healthy female, age 44. We used an Esaote MyLabFive ultrasound imaging machine approved for many applications including cephalic (brain) imaging. We used the default settings for adult transcranial imaging, but instead of a transcranial probe we used a linear probe for muscle-skeletal examination set at 7.5 MHz frequency. Acoustic power was set to 1.0. The temporalis muscle shows the typical echogenic pattern of striated muscles. The temporal squama appears as an hyper-echogenic (white) irregular line of about 1.5 mm thickness. The meninges and the cortex can be visualized.

Fig. 2 A shows the typical sonographic pattern of striated muscles in the region of the temporalis muscle; the thickness of the relaxed muscle from the aponeurosis to the temporal squama was about 4.6 mm (Fig. 2A). As expected, the thickness of the muscle increased during voluntary contraction of the muscle, reaching a thickness of about 5.7 mm (Fig. 2B).

Fig. 3A shows in-depth focalization on the meninges and the cortex. The meninges appeared as a well organized array of layers of about 3 mm thickness. The sub-arachnoid space appeared as a linear "track" with two parallel hyper-echogenic (white) stripes delimiting an anechogenic (black) linear space. Anechogenicity can be attributed to the presence of a thin film of liquor (Fig. 3B). Fig. 3B clearly shows the anatomical localization of the sub-arachnoid space that runs parallel to the temporal squama, approximately in between the meninges and the cortex. The thickness of the sub-arachnoid space as a whole was around 0.5 mm (Fig. 3A), whereas a zoomed-in image of the sub-arachnoid space (Fig. 3C) seems to indicate that the thickness of the liquid film was about 0.2 mm.

The thickness of the cortex was 3.8 mm (Figs. 3A and 4A). This type of thickness and the anatomical positioning of the probe led us to hypothesize that we were observing the temporal areas designated as TG and TE, *i.e.* those areas involved in the control of eye movements and balance in standing position (area TE), social behavior, mood and decision making (area TG).

The spatial resolution and the ability to visualize sub-millimetric structures (Fig. 4B, zoomed-in image of the cortex), led us to hypothesize that the linear structures (alternate gray and white stripes) parallel to the sub-arachnoidal space could be referred to the well known neuronal layers of the cortex (Molnár, 2011). It can be

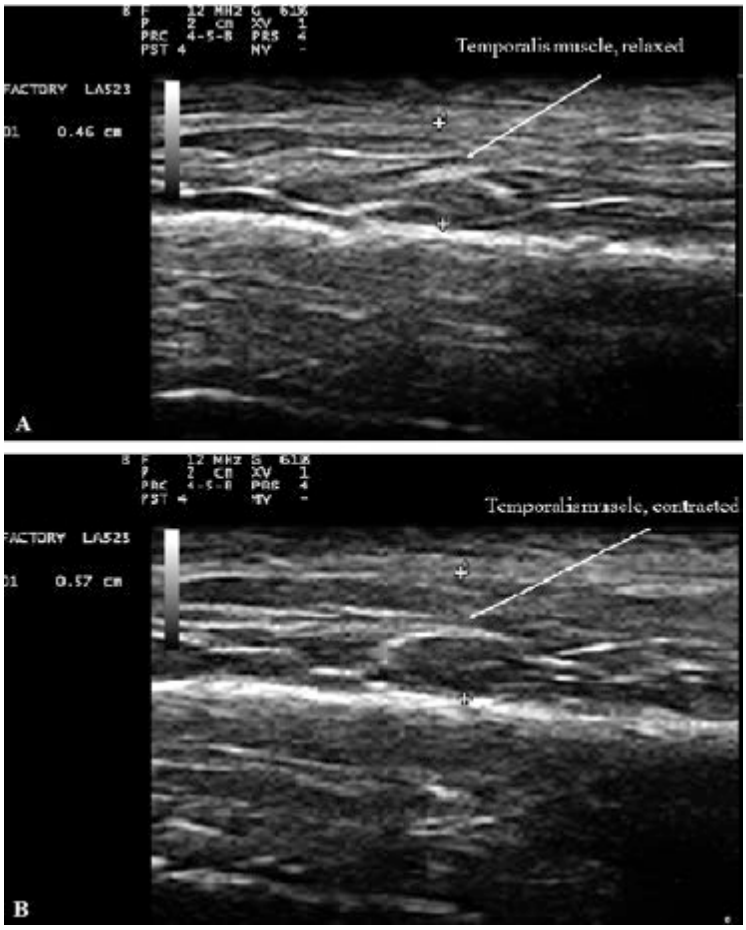

Figure 2 - Thickness of the temporalis muscle. Subject: healthy female, age 44. A - relaxed: 4.6 mm. B - contracted: 5.7 mm.

hypothesized that the white (hyper-echogenic) stripes evidenced in zoomed-in Fig. 4B correspond to areas with complex and irregular cytological architecture such as that typical of those layers characterized by high density of irregularly shaped neuronal bodies. It is worth noticing that the echogenic pattern shown in Fig. 4B resembles that of the Nissl histologic staining that evidences cell bodies of neurons.

Close observation of brain movements during examination revealed the pulsatile brain movements associated with the cardiac cycle that have been described mainly using MRI techniques (Greitz *et al.*, 1992), even though is worth noticing that the first in vivo measurement of brain movement was achieved by ultrasounds (de Vlieger and Ridder, 1959). In addition to the typical pulsatile movements, we also observed a rhythmic movement that was associated with the respiratory cycle. Fig. 5 shows the combined thickness of the meninges and the cortex at the end of forced voluntary

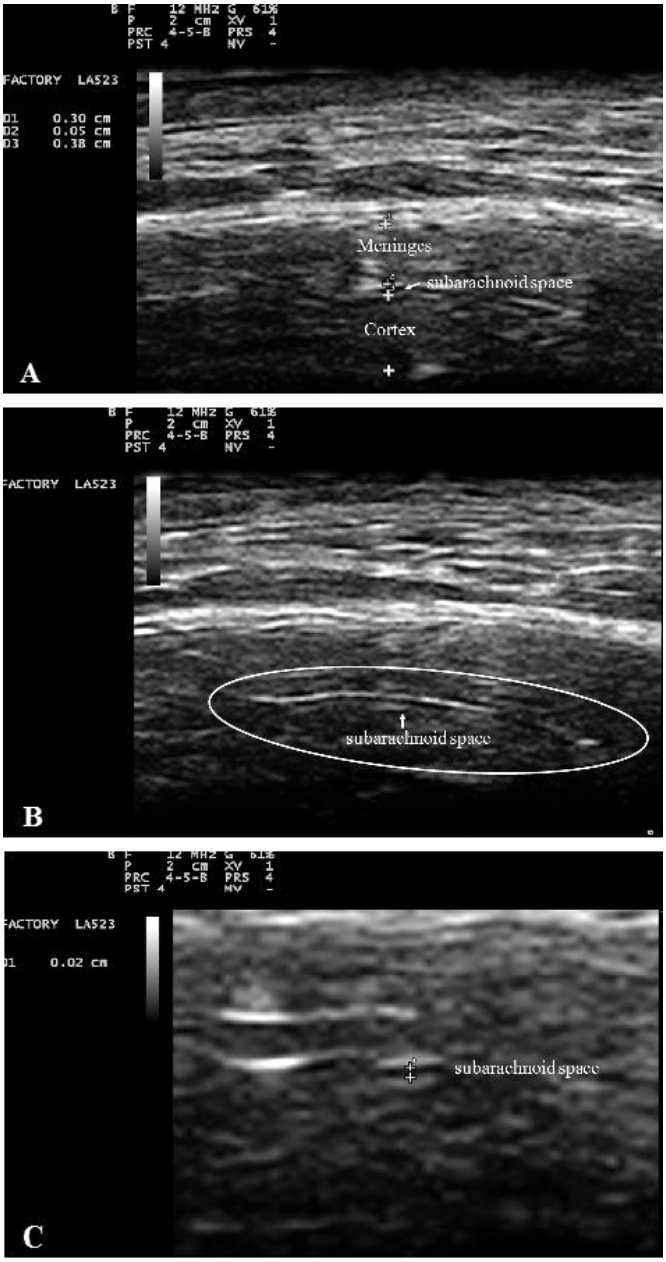

Figure 3 - In-depth focalization on the meninges and the cortex. Subject: healthy female, age 44. A - the meninges appear as a well organized array of layers of about 3 mm thickness. The sub-arachnoid space (white arrow) is identified by two hyper-echogenic (white) stripes sandwiching an anechogenic (black) space containing liquor. B - In-depth focalization on the sub-arachnoid space. C - Zoom-in on the sub-arachnoid space. Zooming-in was performed during the exam using the standard feature of the ultrasound imaging machine. The liquor film appears as an anechogenic (black) space of about 0.2 mm.

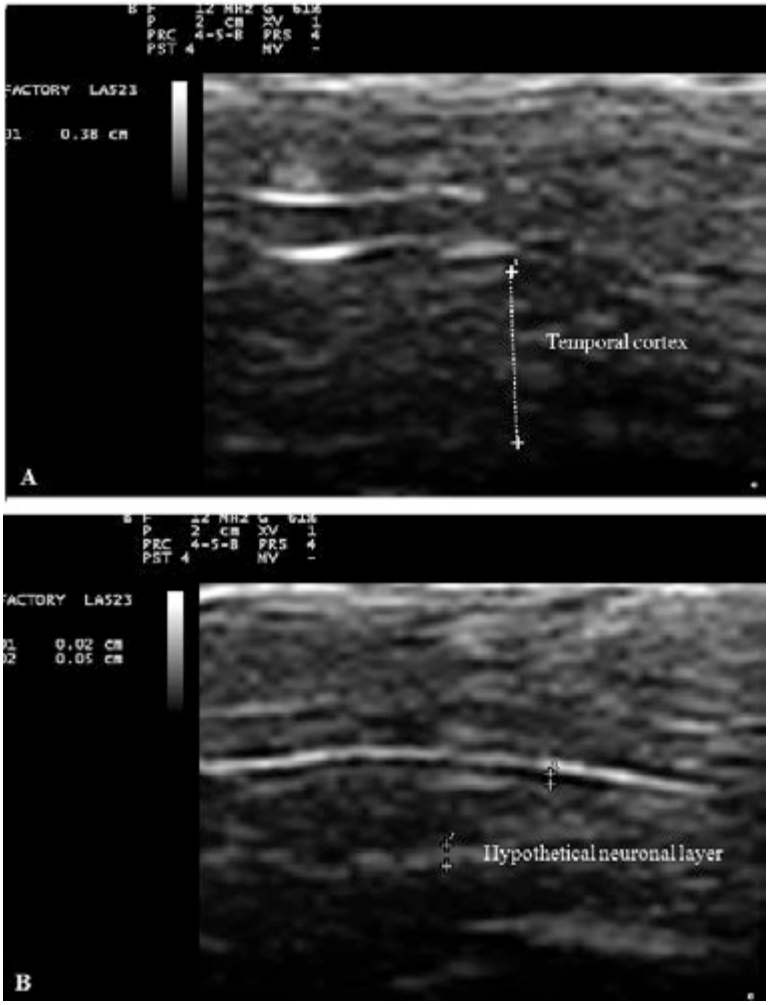

Figure 4 - Zoom-in on the cortex. Subject: healthy female, age 44. A - The neuronal layers of the temporal cortex (3.8 mm total thickness) appear as alternate layers of hyper- and hypo-echogenic structures. The thickness of the cortex corresponds to that of the TE and TG areas. B - An hyper-echogenic stratum, putatively corresponding to a cortical neuronal layer of 0.5 mm is evidenced.

exhalation (Fig. 5A, thickness 7.3 mm), and at the end of forced voluntary inhalation (Fig. 5B, thickness 6.7 mm). These results are consistent with the observation by Turner *et al.* (1998) who described respiratory pulsations as non-random noise components of functional MRI of the human brain.

In addition to visualization of the meninges and the brain cortex, with the type of setting adopted here and using the common color-Doppler features of the machine, we could also observe arterial vascularisation of the meninges and of the cortex and pulsating arteries of less that one mm diameter could be easily visualized (Figs. 6A and B).

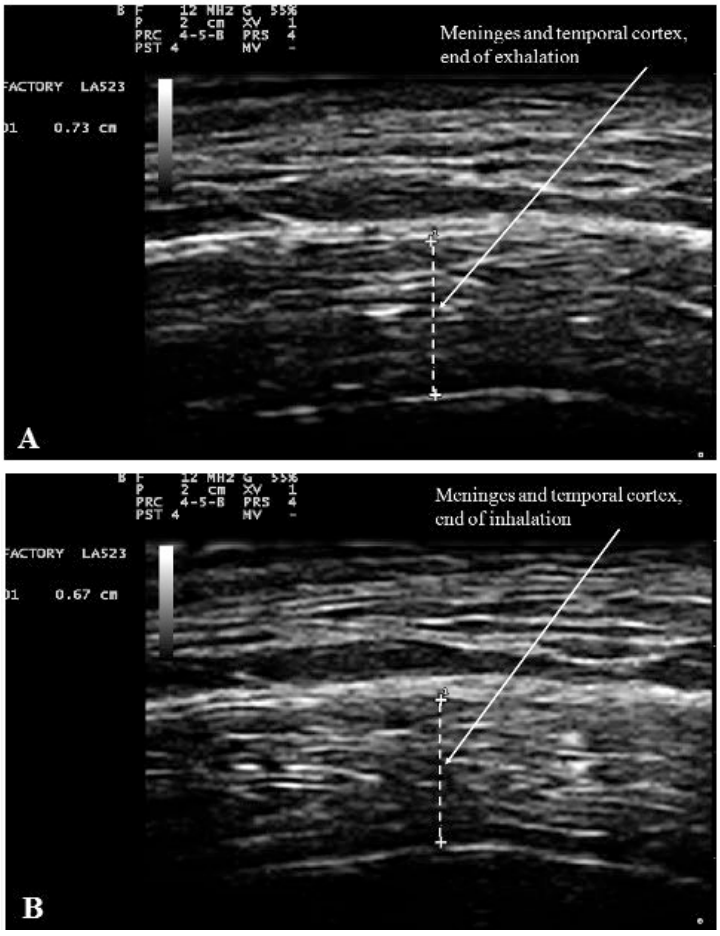

Figure 5 - Thickness of the meninges and the cortex at the end of forced voluntary exhalation (A), and inhalation (B). Subject: healthy female, age 44.

Figs. 1-6 depict the anatomical structures of one single subject, *i.e.* one of the Authors, an healthy female aged 44. In order to assess the reproducibility of the technique, we performed the same type of examination in 5 additional subjects of different gender and age, all of them among the Authors of this study. Since the goal of this examination was the assessment of reproducibility and not the optimal visualization of the anatomical structures, we used the same identical setting and depth of focus for all the subjects. Gain was set to 52% for all subjects. Fig. 7, panel A, refers to the same subject of Figs. 1-6. Gender and age of the other subjects is indicated in the figure as well as in the legend. It is evident that the images are quite comparable and the anatomical structures are recognizable in all subjects. Only the image depicted in panel F is less than optimal; it refers to a male, aged 57, who was the operator and had to perform the exam on himself and, at the same time, operate the machine.

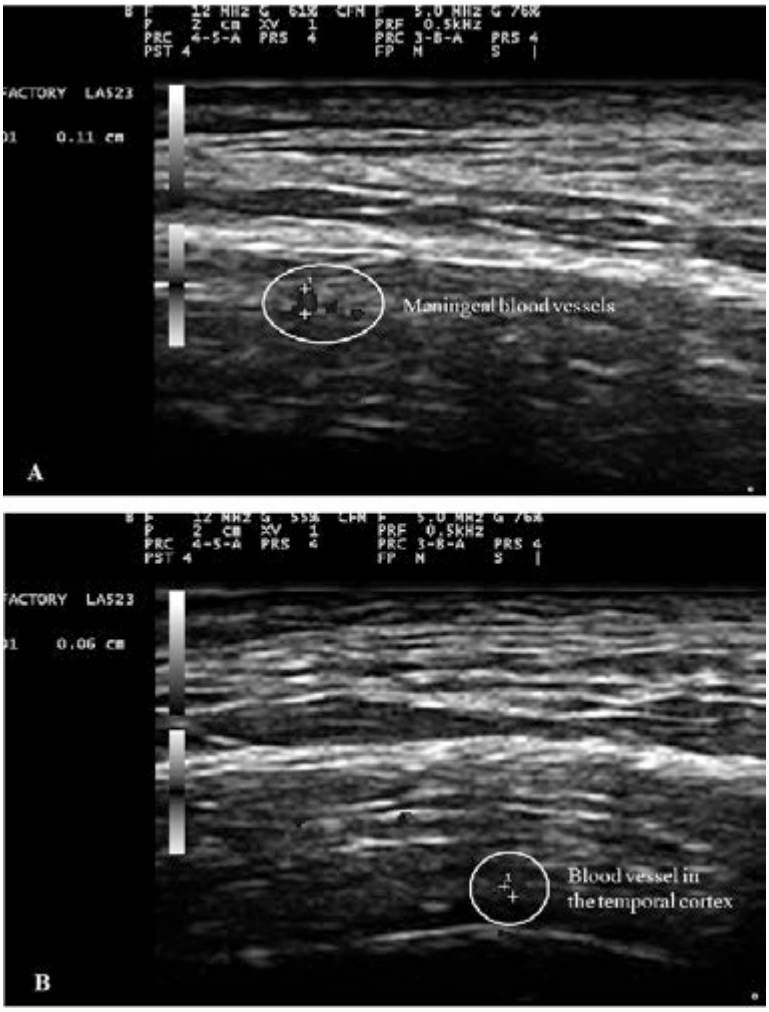

Figure 6 - Pulsating arterial blood vessels in the meninges (A), and in the deep temporal cortex (B). Subject: healthy female, age 44.

Discussion

Transcranial sonography has been used in the past to visualize brain structures such as the substantia nigra, the lenticular nuclei, as well as to measure the width of the third ventricle (Kostić *et al.*, 2012), and this technique has found application in the study of pathological changes associated with neurodegenerative diseases with particular reference to Parkinson's disease (Izawa Okawa and Miwa, 2012). However, in the majority of these studies, small probes dedicated to transcranial sonography were used and the setting was adjusted to allow visualization of the deeper brain

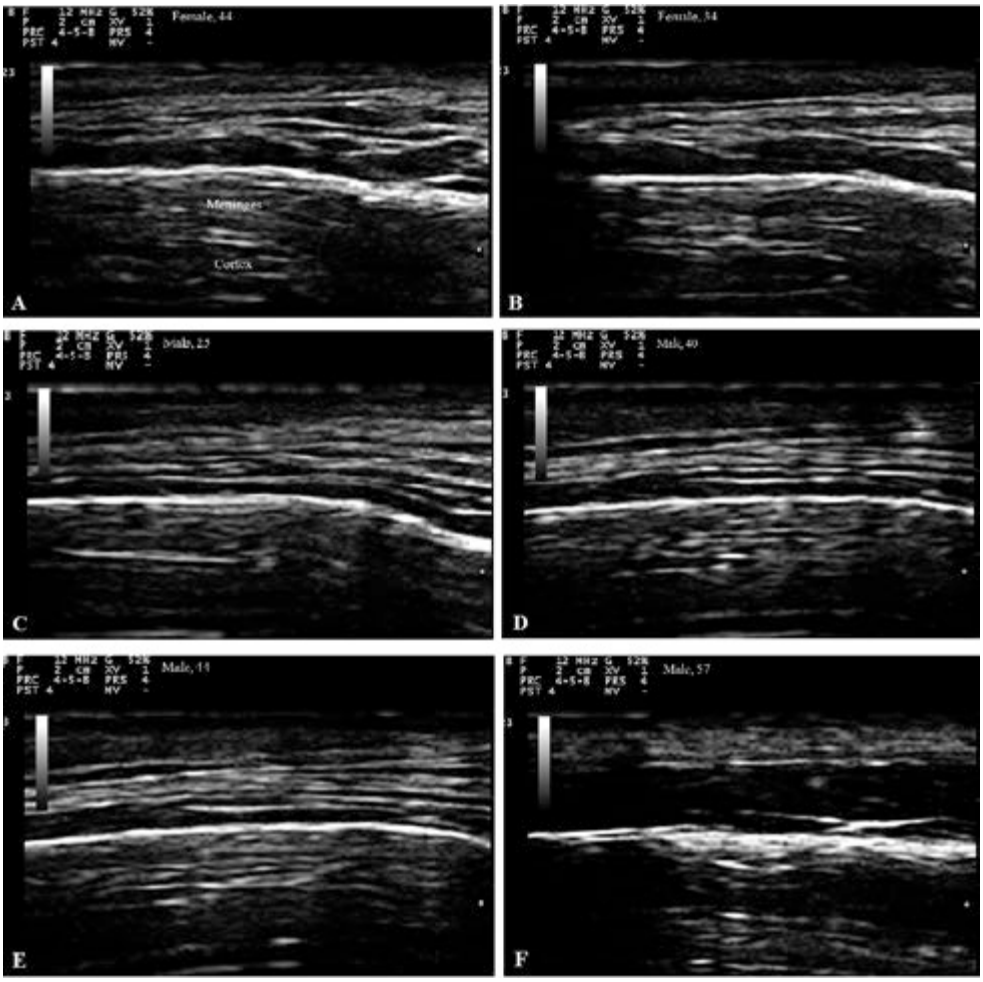

Figure 7 - Two dimension image of the temporal region obtained by transcranial sonography in healthy subjects of different gender and age. A: Female, age 44. B: Female, age 34. C: Male, age 25. D: Male, age 40. E: Male, age 44. F: Male, age 57.

structures, thus preventing the study of the most superficial areas of the cortex. One very recent study used a technical approach to transcranial sonography very similar to the one described here with the purpose of determining the effects of ultrasounds on mental status, and the images presented in a poster deriving from such a study appear very similar to those presented by us (Hameroff *et al.*, 2012), even though these Authors did not study the structures that we observed.

From the perspective of the study of the evolution of the human brain, we hypothesize that the results presented here raise the possibility of using transcranial sonography as a tool for comparative analyses of the temporal region between

humans and other primates. In fact, in recent years the cost of ultrasound imaging machines is significantly decreased and a good quality apparatus can be now easily purchased for research purposes in the field of anthropology.

Furthermore, in addition to its applications in the study of brain evolution, the procedure of transcranial sonography described here can also be used in clinical medicine to study in detail the cerebral cortex with particular reference to the gray matter of the temporal lobe, and for the study of vascularisation of the meninges. Significant neuroanatomical changes occur in neurodegenerative diseases (Romito-DiGiacomo *et al.*, 2007; Puri *et al.*, 2012), which from the point of view of evolution of the human brain may be defined as "phylogenic diseases" (Hughlings Jackson, 1884; Roofe and Matzke 1968; Sarnat and Netsky 1981; Rapoport, 1988, 1989) according to principle of "integrated phylogeny" of the primate brain (Rapoport, 1990) because of their possible relation to evolution. Therefore, transcranial sonography may prove a simple and inexpensive tool to assess these changes and monitor progression of the diseases as well as morphological changes associated with treatments. In particular, we suggest that transcranial sonography may prove useful in studying the following morphological brain features that are known, or hypothesized to be, altered in different neurological diseases:

1. Thickness of the cortex.
2. Neuronal layer arrangement.
3. Thickness and organization of the meninges.
4. Vascularization of the meninges and the cortex.
5. Brain movements.

The study of vascularization might also prove useful in assessing the putative inflammatory status that is hypothesized to be associated with Myalgic Encephalomyelitis (Carruthers *et al.*, 2011). In fact, we presume that in the presence of a chronic inflammatory condition, the brain vascularization pattern might appear at the sonography examination similar to what is observed during the course of thyroiditis (Enăchescu *et al.*, 2006).

In conclusion, the inherent safety of the technique as well as the absence of discomfort make this procedure quite promising for the study of the brain in human and non-human primates.

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