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## **Ultrafast Doppler for Neonate Brain Imaging**

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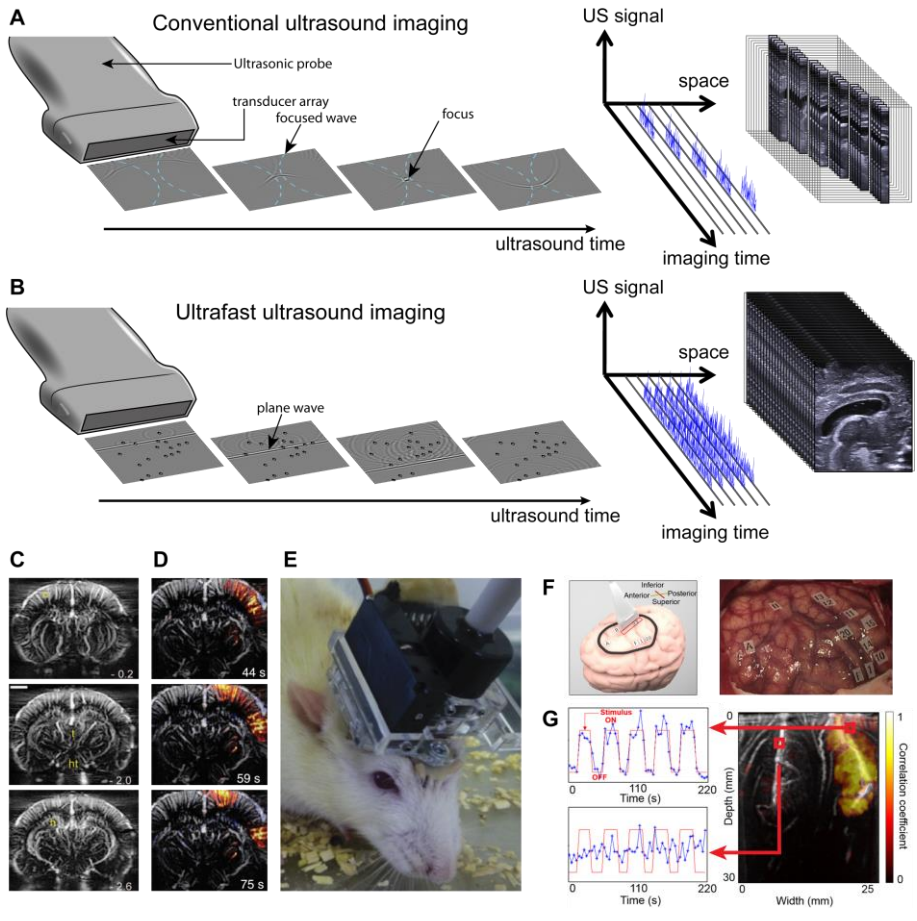
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### ***Introduction to Ultrafast Doppler imaging***

The year 1999 was a major turning point for Ultrasound imaging with the invention of Ultrafast Imaging (Sandrin et al., 1999). By reaching frame-rates up to several thousands of images per second, it enabled to image natural phenomena, like shear wave propagation (Bercoff et al., 2004; Sandrin et al., 2002; Tanter et al., 2008), that were previously invisible to conventional techniques limited to a frame-rate of about 100 Hz. Ultrafast Ultrasound Imaging relies on a new paradigm for ultrasonic emissions : instead of using focused beams to build line-by-line images as it is done in conventional ultrasound imaging (Figure 1 A), plane wave are emitted through the tissues to build image-by-image (Figure 1 B) ultrasonic movies at an ultrafast framerate (up to several tens of kHz) (Montaldo et al., 2009). This ultrasonic emission strategy enables to acquire a considerably larger amount of information on the propagation medium compared to conventional ultrasound (Figure 1), and was found of special interest and effectiveness for detecting red blood cell motion with higher sensitivity and quantification capabilities (Bercoff et al., 2011). This combination of high spatiotemporal resolution and very high sensitivity is the key of the Ultrafast Doppler (UfD, Ultrafast Imaging applied to blood flow imaging) performance (Demene et al., 2015). These potentialities has been applied in various clinical applications ranging from cardiac (Hansen et al., 2016; Maresca et al., 2017; Osmanski et al., 2012) to carotid (Ekroll et al., 2014; Lenge et al., 2015; Provost et al., 2014), an even ophthalmologic imaging (Urs et al., 2016).

Among the organs of interest for Ultrafast Doppler imaging, the brain is probably the one showing the most stunning possibilities for this new imaging modality. In a seminal publication introducing functional Ultrasound (fUltrasound), it was shown that Ultrafast Doppler could be used in trepanned rats for imaging the cerebral vasculature with a unprecedented sensitivity (Figure 1C), and that the technique was able to detect the small local cerebral blood volume changes in the barrel cortex when stimulating one of the rat whiskers (Macé et al., 2011). In the same paper, spatiotemporal dynamics of local hemodynamic changes related to the propagation of an epileptic seizure were captured via Ultrafast Doppler and showed cortical spreading depression waves at a time and space scale no other

modality was able to describe before (Figure 1D). This was the entry point of fUltrasound in the neuroimaging field, with a large scope of preclinical applications in both anesthetized and awake animals (Figure 1E): studies has been conducted on the rat olfactory tract (B. F. Osmanski et al., 2014), visual system (Gesnik et al., 2017), spatial representation (Sieu et al., 2015), visual system of the pigeon (Rau et al., 2017), auditory system of the ferret (Demené et al., 2016). In most of these animal studies a thinned skull surgery or a trepanation was needed to enable the penetration of the ultrasound waves, and the first in-human proof of concept (Imbault et al., 2017) used a similar approach to circumvent the obstacle of the thick human skull (Figure 1F). Imbault et al. showed that they were able to precisely and in-depth map the functional areas implicated in motor and somatosensory tasks on the imaged portion of the brain, thus giving valuable insight to the surgeon for tumor removal.



**Figure 1.** A. Conventional ultrasound imaging. The transducer array is used to emit focused waves in the propagation medium (left). For Doppler imaging, this process has to be repeated several times in order to identify moving scatterers (namely the red blood cells) before electronically moving to another location in space. The image is then build line sets by line sets, resulting in fragmented information across space and time, as depicted on the graph on the right. B. In ultrafast ultrasound imaging, plane waves are sent into the propagation medium, and the echoes backscattered from all scatterers are collected at once. The ultrasonic movie is therefore build images by images, resulting in far more information. C. Rat cerebral vascular network imaged via Ultrafast Doppler. D. Propagation of epileptic seizure imaged in fUltrasound using Ultrafast Doppler (C & D adapted from (Macé et al., 2011)). E. Implantation of an ultrasonic probe for fUltrasound on an awake and freely moving rat head. Adapted from (Sieu et al., 2015). F. Proof of concept of fUltrasound imaging on humans during open-skull surgery, the probe is directly applied on the brain. G. Ultrafast Doppler signal changes in the sensory cortex (top) and adjacent area (bottom) during stimulation of the lips of the patient, the map on the right shows the correlation of this signal with the stimulation pattern. (F & G adapted from (Imbault et al., 2017)).

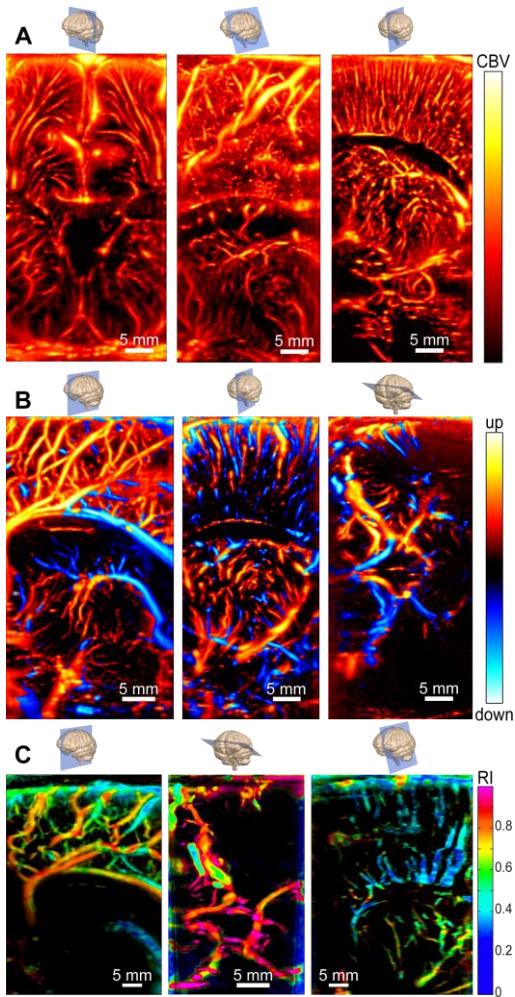
### ***Ultrafast Doppler for Imaging the Neonatal Brain***

Ultrafast Doppler and fUltrasound takes advantage of the fontanels, anatomical windows specific to the neonates that give a natural way of circumventing the problem of the skull penetration for ultrasound, and that boosted the translation to clinics for brain imaging in neonates with very promising perspectives.

Ultrafast Doppler enabled three major advances for neonate cerebral imaging: imaging of usually undetected blood vessels, gathering imaging and quantification in a single ultrasonic modality, and functional imaging of the brain based on the monitoring of local subtle hemodynamics changes.

The first aspect was illustrated in a paper published in 2014 (Demené et al., 2014) showing that Ultrafast Doppler could be translated to clinics in neonatology. Brain imaging through fontanels gives access to many structures of the brain including notably cortex, subplate, white matter and periventricular zones, and basal ganglia, and reveal microvessels down to the arteriole and venule scale, as illustrated in Figure 2A. For such images, a 6MHz probe is used, giving a good tradeoff between a 200 µm resolution and an up to 8 cm penetration. In coronal views, medullary vessels as well as thalamo-striate arteries are usually depicted (left image). In parasagittal planes, small cortical penetrating arteries are observed (center image), and in some cases the cortical watershed can clearly be identified (right image). UfD acquisitions keeping track of the blood flow complete information in every pixel, directional UfD images can be derived from the ultrafast cineloop, as shown in Figure 2B (left: the venous network underneath the ventricle is clearly depicted, middle: in parasagittal planes small thalamic and cortical arterioles and venules are easily discriminated, right: the circulation pattern in the Willis polygon is well defined).

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**Figure 2.** A. So-called Power Doppler images obtained via Ultrafast Doppler through the anterior fontanel. From left to right: coronal view, tilted parasagittal view, parasagittal view. B. Directional Power Doppler images, obtained by using the speed information (up or down) contained in each pixel. From left to right: medial sagittal view, parasagittal view, transtemporal transverse view (mastoid fontanel for imaging Willis polygon and cerebellum). C. Resistivity mapping based on Ultrafast Doppler acquisition. In big arteries the Resistivity Index (RI) is between 0.8 and 1 (left and center image), whereas RI is lower in small lenticulostriate arteries (~0.6) and very low (<0.3) in veins. Original data and images adapted from (Demené et al., 2014).

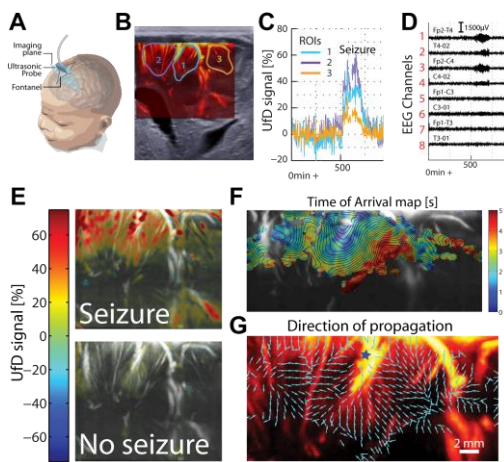
The second aspect, i.e. gathering imaging and quantification in the same modality, is illustrated in Figure 2C under the form of Resistivity Index mapping. As shown in Figure 1, in conventional focused imaging the number of temporal adjacent samples in each pixel is intrinsically limited by the need to electronically sweep the whole field of view with the ultrasonic beam, whereas in Ultrafast imaging this number is very large, added to the fact that samples in all pixels are synchronous. This enables the precise quantification of blood flow speeds based on efficient Fourier analysis in all pixels at the same time. The Resistivity Index (Pourcelot, 1976) can then be calculated in every pixel based on the maximum and minimum speed along the cardiac cycle, and mapped on the whole field of view (Demené et al., 2014). This approach could dramatically change the clinical practice, especially for neonates, not only because it provides much broader data on hemodynamics compared to the pulse wave single location measurement after color flow imaging scanning but also it opens the way to Resistivity Index monitoring across long time scales without operator-dependent measurements.

#### ***Functional Ultrasound in Human Neonates***

Functional Ultrasound is the most recent and innovative aspect of the use of UfD in human neonate. Using a miniaturized custom-made ultrasonic probe, maintained on the neonate anterior fontanel by a special headset (Figure 3 A), (Demene et al., 2017) showed that fUltrasound by UfD was a modality of high interest. First, they could differentiate two stages of sleep (quiet sleep and active sleep) based on the fluctuations of the UfD signal, and confirmed by a simultaneous 8-channel EEG recording. Second, they could map cerebral blood volume fluctuations in neonates' brain during epileptic seizures. These latest findings were revealed in pathological cases of abnormal cortical development leading to uni-hemispheric seizures (due to ipsilateral lesions, e.g. hemimegalencephaly or cortical dysplasia) (Figure 3 B, D). UfD was able to show this confinement, with high fluctuation of the UfD signal in the pathologic hemisphere (Figure 3 C, E). Furthermore, the spatiotemporal resolution of the imaging technique enabled them to observe and analyze waves of vascular activity propagating at



speeds of the order of mm/s, during the inter ictal period characterized by spikes of electric activity (Figure 3 F,G).



**Figure 3.** A. Schematics showing the disposition of the ultrasonic probe on the anterior fontanel. B. UfD image overlaid on the B-Mode ultrasonic image showing the cortical structures and position of the ventricles in a neonate with hemimegalencephaly (right side, ROI 1 and 2). The 3 ROIs are used for spatially averaging the UfD signal. C. Evolution in the Ultrafast Doppler signal in the 3 ROIs during an epileptic seizure taking place mostly in the right cerebral hemisphere. D. Simultaneous 8 channel EEG recording showing ictal activity in the right hemisphere. E. Relative changes in UfD signal during and after the seizure, the color represents the relative increase or decrease of the UfD signal in percentage. F.G. By analyzing the UfD signal during inter ictal period of electric spike activity, the author showed that propagation of vascular waves could be characterized in terms of time of arrival maps (F) and direction of propagation (G). Adapted from (Demene et al., 2017).

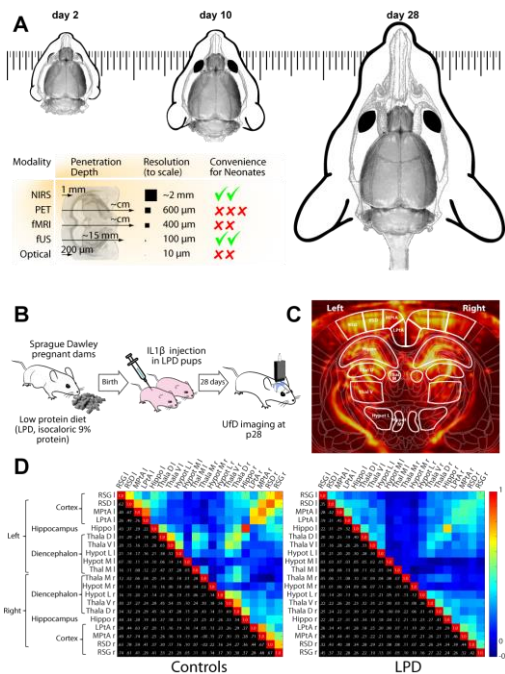
This first proof of concept that fUltrasound is feasible in human neonates opens a large field of applications for both preclinical and clinical imaging. Cerebral functional imaging with a common methodology and spatiotemporal resolution across both contexts (neonates and animal models) will be of utmost importance for developmental studies as well as pharmacological investigations.

Feasibility and relevance should also be balanced with a strict safety profile when implementing a new imaging modality, especially in very vulnerable neonates exposed to prolonged high intensity ultrasound scanning. Although routine conventional cerebral ultrasound scanning in infants is considered safe, Doppler imaging (especially for longer duration) has been critically reviewed regarding the potential issues of prolonged high intensity scanning (Ang et al., 2006) in the developing brain reported in rodents. In our clinical investigation, acoustic amplitudes and intensities remained below the Food and Drug Administration limitations for ultrasonic diagnostic imaging (FDA, 510 k, Track 3). Moreover, in order to be cautious, we chose a very restrictive approach as the Mechanical Index and the spatial-peak time-averaged intensity  $I_{spta}$  used in our investigation were kept to very low values (respectively  $MI = 0.85$ ,  $I_{spta} = 43,5 \text{ mW/cm}^2$ ) compared to the FDA accepted limits (respectively  $MI < 1.9$  and  $I_{spta} < 720 \text{ mW/cm}^2$ ). Such lower acoustic values are possible without compromising the imaging quality and sensitivity thanks to the coherent recombination of backscattered signals from different transmissions and the better spatio-temporal spreading of acoustic energy in tissue when using plane ultrasonic waves instead of conventional line per line focused beams, thus reducing the amount of energy deposit.

#### ***Impact and perspectives in neonatal translational studies***

It is worth noticing that the imaging modalities widely used in human imaging (fMRI, PET) are not the one offering the best spatio-temporal resolution for preclinical imaging, and this is even exacerbated for developmental studies in preclinical models of human diseases since brain of rodent pups are really small (Figure 4 A). Other techniques widely used for animal imaging (optical techniques, implanted electrodes, laser speckle imaging, etc) are too inconvenient or offering too poor penetration depth for human neonate imaging. fUltrasound using UfD fills this gap and offers a combination of penetration and spatiotemporal resolution unique for neonatal translational studies (Figure 4 A). Moreover, imaging through the fontanel or through the uncalcified skull of young rats and mice show similar ease of implementation. Proof of concepts of what can be achieved in the evaluation of pharmacologic

effect of drugs using fUltrasound have already been done. In a method paper, (B.-F. Osmanski et al., 2014) showed that fUltrasound could be used as a tool to study cerebral connectivity using seed based resting state correlations between different areas of the rat brain. Those correlations gathered in so called “connectivity matrices” exhibited strong values of correlations on the anti-diagonal (interhemispheric connectivity) as well as on the adjacent diagonals (intra-hemispheric connectivity). This tool has been already used to study the drop of cortical connectivity in a rat model of intrauterine growth restriction (Figure 4 B) and to assess *in vivo* the consequences of fetal growth restriction on brain function (Rideau Batista Novais et al., 2016). Using assessment of cerebral connectivity at day p28 between selected cerebral areas (in the cortex, hippocampus, thalamus and hypothalamus, see Figure 4 B), correlation matrices showed abnormally decreased inter an intra hemispheric connectivity, supported by conventional structural MR brain imaging and confirmed at the histological level using myelination quantification.



**Figure 4.** A. Schematics depicting to scale the rat head and brain size at different ages, underlying the potentialities of fUltrasound for translational and developmental studies in preclinical settings compared to other modalities in terms of penetration and resolution (brain slice and pixel size are to scale). B. Use of fUltrasound to assess cerebral connectivity in an intra-uterine growth restriction model. The pregnant dam is fed with a low protein die (LPD, isocaloric 9% protein), then the pups received an injection of interleukine IL1 $\beta$  to mimic post birth neuro-inflammation, and fUS connectivity imaging is conducted on the young rat at post-natal age 28. C. The rat cerebral vasculature is subdivided in functional relevant areas whose spatially average UfD signal time course will be correlated. D. Matrices depicting these correlations for control rats (left) (N=3) and LPD+ IL1 $\beta$  rats (right) (N=3). (Original data).

The impact of developing a new modality of brain imaging is high in the field of perinatal medicine. Indeed, prematurity and perinatal asphyxia could lead to neurocognitive deficits and subsequent handicaps, major concerns for public health because they affect infants and have lifelong consequences for their health and wellbeing. Strategies that screen high-risk neonates through novel markers of brain function and accurate brain monitoring, early after birth would have immediate and significant benefits in two major fields:

- Improving better knowledge on functional prognosis following perinatal brain injury, and about brain damage progression within the first year in high-risk population of neonates.

- Identifying sensitive markers of early brain damage in patients who could benefit from the neuroprotective strategies planned to be tested in near future clinical trials (Parikh and Juul, 2017).

### **Conclusion**

fUltrasound has been introduced as a genuinely new modality in the field of neuroimaging preclinical models of central nervous system diseases, and clinical feasibility and relevance in human neonates has been recently demonstrated. This new tool should be ready to be introduced in the neonatal intensive care units within 3-5 years to detect abnormal brain activity associated with injuries caused by perinatal adverse events such as perinatal asphyxia and prematurity. It could also be of crucial importance in eligibility criteria in clinical trials for drugs aimed at protecting the brain. fUltrasound is also a new technique equally important for neuroscientists who want to study normal brain development and the developmental origins of diseases such as autism and make much stronger predictions in the future.

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