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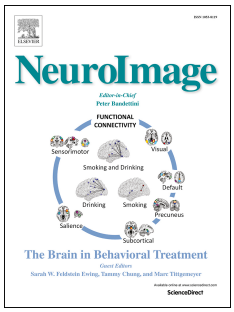

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Ultrafast Doppler for Neonatal Brain Imaging

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Abstract

The emergence of functional neuroimaging has dramatically accelerated our understanding of the human mind. The advent of functional Magnetic Resonance Imaging paved the way for the next decades' major discoveries in neuroscience and today remains the "gold standard" for deep brain imaging. Recent improvements in imaging technology have been somewhat limited to incremental innovations of mature techniques instead of breakthroughs. Recently, the use of ultrasonic plane waves transmitted at ultrafast frame rates was shown to highly increase Doppler ultrasound sensitivity to blood flows in small vessels in rodents. By identifying regions of brain activation through neurovascular coupling, Ultrafast Doppler was entering into the world of preclinical neuroimaging. The combination of many advantages, including high spatio-temporal resolution, deep penetration, high sensitivity and portability provided unique information about brain function. Ultrafast Recently, Ultrafast Doppler imaging was found able to non-invasively image the spatial and temporal dynamics of microvascular changes during seizures and interictal periods with an unprecedented resolution at bedside. This review summarizes the technical basis, the added value and the clinical perspectives provided by this new brain imaging modality that could create a breakthrough in the knowledge of brain hemodynamics, brain insult, and neuroprotection.

Introducing Ultrafast Doppler as a new imaging modality

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 frame-rate (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 spatio-temporal 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 UfD 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 UfD 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, spatio-temporal dynamics of local hemodynamic changes related to the propagation of an epileptic seizure were captured via UfD 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.

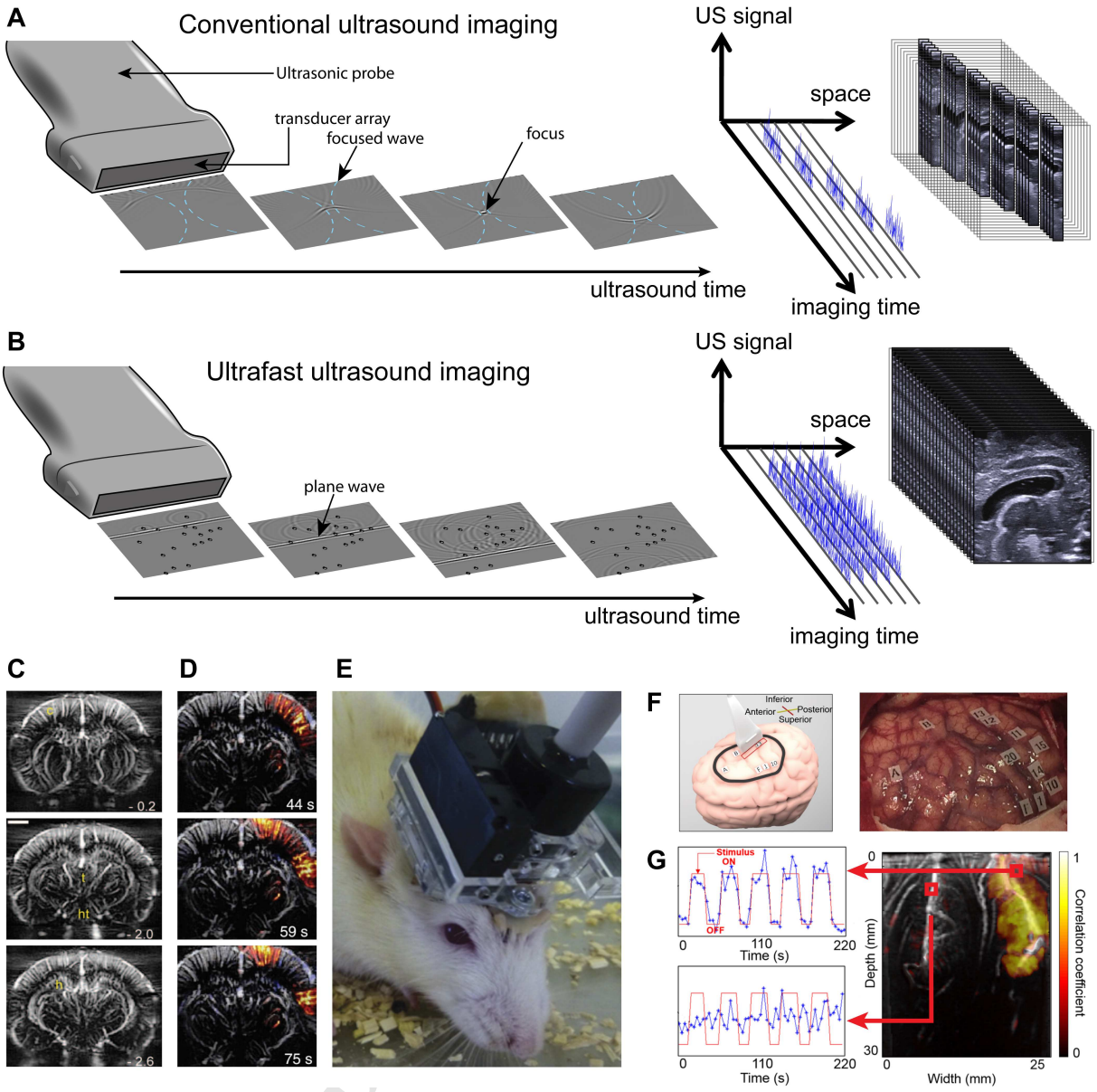

Figure 1. ***A.*** *Conventional ultrasound imaging. The transducer array is used to emit focused waves in the propagation medium (left). For Doppler imaging, this process has to be repeated several times in order to identify moving scatterers (namely the red blood cells) before electronically moving 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 UfD.* ***D.*** *Propagation of epileptic seizure imaged in fUltrasound using UfD (**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.*** *UfD 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)).*

Imaging the neonatal brain using UfD

UfD 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.

UfD enabled three major advances for neonate cerebral imaging: imaging of usually undetected blood vessels, gathering tissue imaging and quantification of its perfusion 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 UfD 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 6 MHz probe is used, giving a good trade-off 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. In parasagittal planes, small cortical penetrating arteries are observed, and in some cases the cortical watershed can clearly be identified. 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.

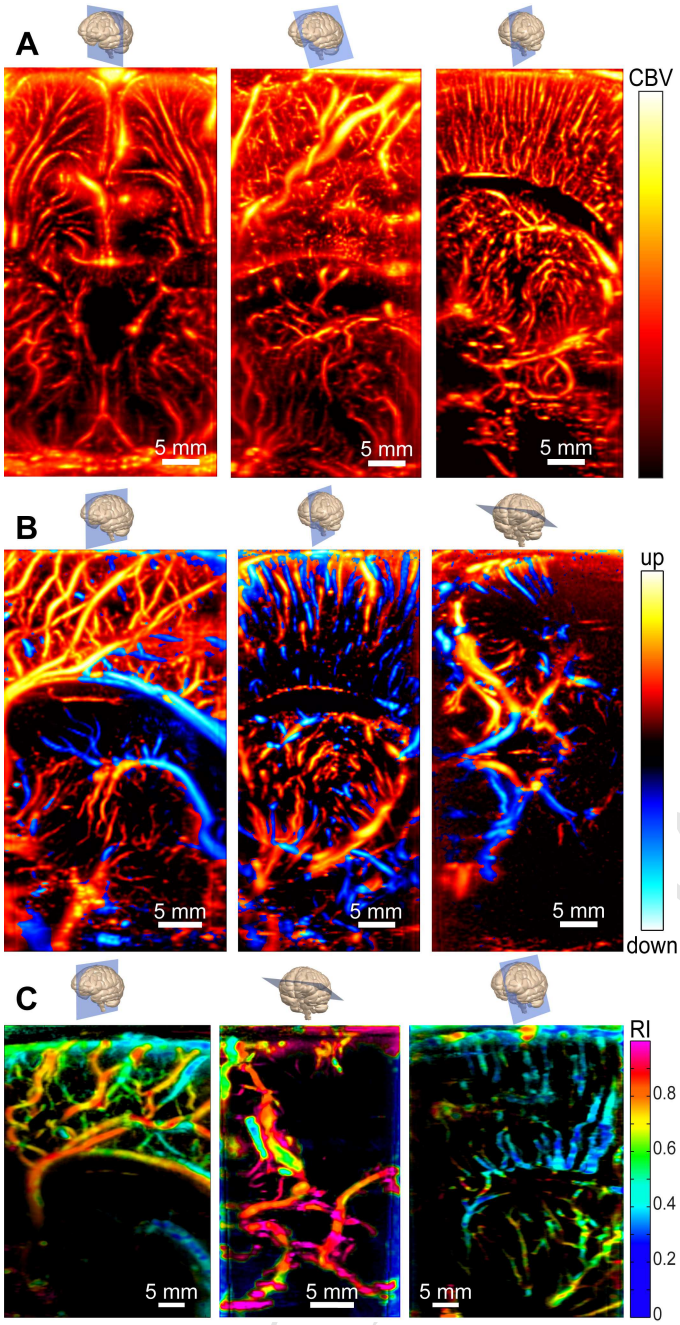

Figure 2. ***A.*** *So-called Power Doppler images obtained via UfD trough the anterior fontanel. From left to right: coronal view, tilted parasagittal view, parasagittal view.* ***B.*** *Directional Power Doppler images, obtained by using the speed information (up or down) contained in each pixel. From left to right: medial sagittal view showing venous network around lateral ventricle, parasagittal view showing small thalamic and cortical arterioles and venules, and transtemporal transverse view through mastoid fontanel for imaging Willis polygon and cerebellum.* ***C.*** *Resistivity mapping based on UfD acquisition. In big arteries the Resistivity Index (RI) is between 0.8 and 1 (left and center image), whereas RI is lower in small lenticuliostriate 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 (RI) 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 RI (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 might dramatically change the clinical practice in the near future, 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 because it opens the way to RI monitoring across long time scales without operator-dependent measurements.

Towards functional Ultrasound in neonates

Functional Ultrasound (fUltrasound) is the most recent and innovative aspect of the use of UfD in human neonate. This new modality was recently tested using a miniaturized custom-made ultrasonic probe, maintained on the neonate anterior fontanel by a special headset (Figure 3 A), (Demene et al., 2017). First, it was able to 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, it was found of interest to 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 spatio-temporal resolution of the imaging technique enabled 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).

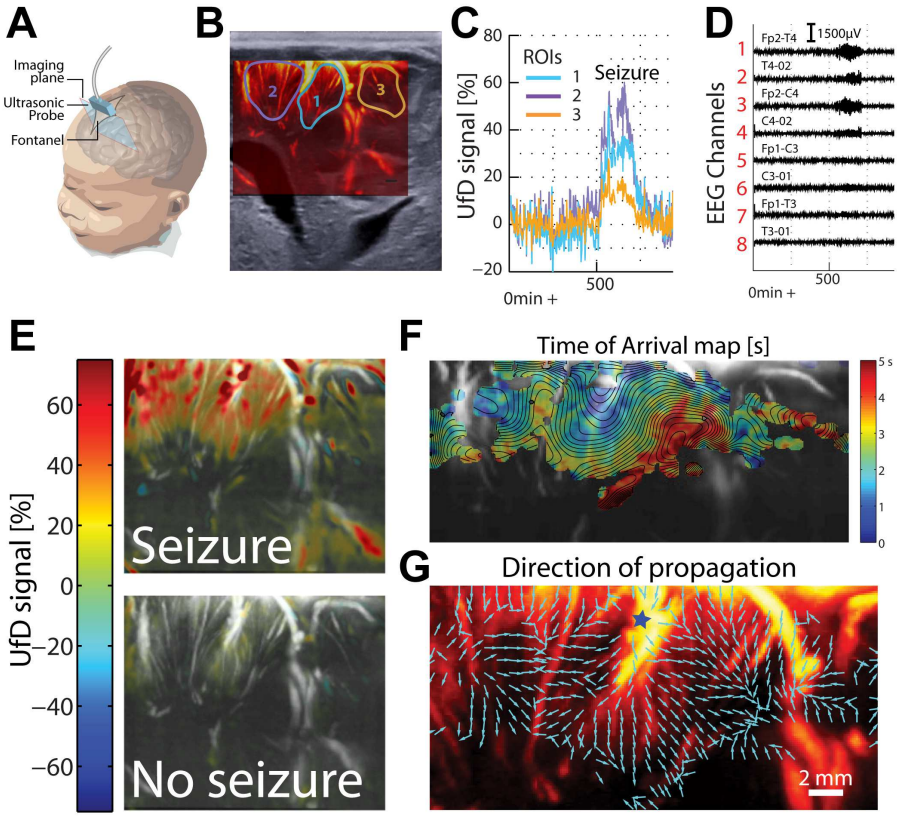

Figure 3. ***A.*** *Schematics showing the disposition of the ultrasonic probe on the anterior fontanel.* ***B.*** *UfD image overlaid on the B-Mode ultrasonic image showing the brain structures of a neonate with right hemimegalencephaly and the 3 ROIs used for spatially averaging the UfD signal.* ***C.*** *Changes in the UfD signal (in %) in the 3 ROIs during an epileptic seizure mostly observed in the right hemimegalencephalic 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 propagation of vascular waves could be identified and 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 demonstrating 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 spatio-temporal resolution both in neonates and animal models will be of utmost importance for developmental studies as well as pharmacological investigations.

Feasibility and relevance should also balanced with 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) have 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 investigations, 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 Ispta used in our investigation were kept to very low values (respectively MI = 0.85, Ispta = 43,5 mW/cm^2) compared to the FDA accepted limits (respectively MI < 1.9 and Ispta < 720 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.

Besides ultrafast imaging, intravascular microbubble contrast agents have been developed to enhance ultrasound echoes leveraging the acoustic impedance mismatch between the gas content and the surrounding blood, and provide functional analyses including real-time acquisition of organ perfusion (Cosgrove, 2006). However its use for brain functional imaging remains poorly sensitive (van Raaij et al., 2011). Various types of bubbles have been developed for imaging purpose or drug and gene delivery (Leinenga, et al., 2016). Despite their promising properties, microbubble contrast agents have been reported to have also bio-effects in the brain, a potentially important concern when imaging premature babies. Indeed, ultrasound pressure can enhance gas diffusion, agent fragmentation into a set of smaller bubbles or displace the microbubble to a blood vessel wall. Insonation of a microbubble can also produce local shear stress that alter biological membranes and facilitate transport (Qin et al., 2009). While the Food and Drug Administration recently approved the use of a US contrast agent for evaluation of liver disorders in the pediatric population, evaluation of the brain using microbubbles remains an off-label practice. Ultrafast imaging modality is therefore

the unique method validated to image the baby brain with high spatio-temporal resolution at bedside.

Impact and perspectives in neonatal translational studies

It is worth noticing that the imaging modalities widely used in human imaging (fMRI, PET) are not those 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 (including optical techniques, implanted electrodes, and laser speckle imaging) are too inconvenient or offering too poor penetration depth for human neonate imaging. fUltrasound using UfD fills this gap by combining deep brain penetration and high spatio-temporal resolution, a unique opportunity for neonatal translational studies (Figure 4 A). Moreover, imaging through the fontanels 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, fUltrasound has been successfully tested to study cerebral connectivity using seed based resting state correlations between different areas of the rat brain (Osmanski et al., 2014). Those correlations gathered in so called “connectivity matrices” exhibited strong values of correlations on the anti-diagonal (inter-hemispheric connectivity) as well as on the adjacent diagonals (intra-hemispheric connectivity). This tool has been shown to have enough sensitivity to detect 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 among 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.

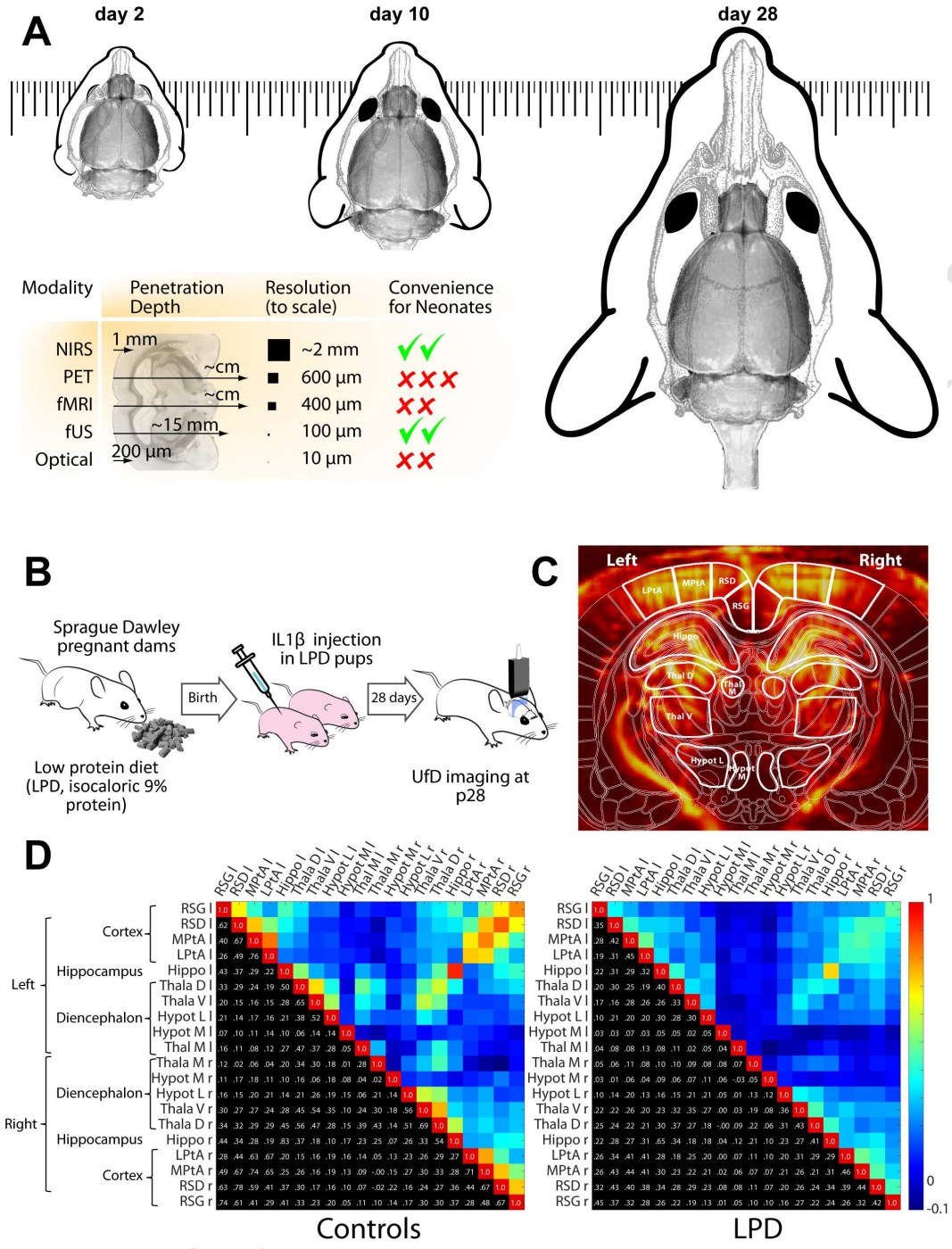

Figure 4. ***A.*** *Schematics depicting to scale the rat head and brain size at different ages, underlying the potentialities of fUltrasound for translational and developmental studies in preclinical settings compared to other modalities regarding penetration depth and spatial resolution (brain slice and pixel size are to scale).* ***B.*** *Use of fUltrasound to assess cerebral connectivity in an intra-uterine growth restriction model. The pregnant dam was fed with a low protein diet (LPD), then the pups received an injection of IL1β to mimic postnatal neuro-inflammation, and fUS connectivity imaging was conducted in rat at the age of post-natal day 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+ IL1β rats (right) (N=3). (Original data).*

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. The potential impact of developing a new modality of brain imaging is therefore high in the field of perinatal medicine. Indeed, strategies that screen high-risk neonates would have immediate and significant benefits by:

- 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).

- Providing accurate brain monitoring in sick neonates early after birth.

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

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.

References

Ang, E.S.B.C., Gluncic, V., Duque, A., Schafer, M.E., Rakic, P., 2006. Prenatal exposure to ultrasound waves impacts neuronal migration in mice. Proc. Natl. Acad. Sci. 103, 12903–12910.

Bercoff, J., Montaldo, G., Loupas, T., Savery, D., Mézière, F., Fink, M., Tanter, M., 2011. Ultrafast compound Doppler imaging: providing full blood flow characterization. IEEE Trans. Ultrason. Ferroelectr. Freq. Control 58, 134–147.

Bercoff, J., Tanter, M., Fink, M., 2004. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. IEEE Trans. Ultrason. Ferroelectr. Freq. Control 51, 396–409.

Cosgrove, D., 2006. Ultrasound contrast agents: an overview. Eur. J. Radiol. 60, 324–330.

Demene, C., Baranger, J., Bernal, M., Delanoe, C., Auvin, S., Biran, V., Alison, M., Mairesse, J., Harribaud, E., Pernot, M., Tanter, M., Baud, O., 2017. Functional ultrasound imaging of brain activity in human newborns. Sci. Transl. Med. 9, eaah6756.

Demené, C., Bimbard, C., Gesnik, M., Radtke-Schuller, S., Shamma, S., Boubenec, Y., Tanter, M., 2016. Functional Ultrasound Imaging of the thalamo-cortical auditory tract in awake ferrets using ultrafast Doppler imaging, in: 2016 IEEE International Ultrasonics Symposium (IUS). Presented at the 2016 IEEE International Ultrasonics Symposium (IUS), pp. 1–4.

Demene, C., Deffieux, T., Pernot, M., Osmanski, B.F., Biran, V., Gennisson, J.-C., Sieu, L.-A., Bergel, A., Franqui, S., Correas, J.M., Cohen, I., Baud, O., Tanter, M., 2015. Spatiotemporal clutter filtering of ultrafast ultrasound data highly increases Doppler and fUltrasound sensitivity. IEEE Trans. Med. Imaging PP, 1–1.

Demené, C., Pernot, M., Biran, V., Alison, M., Fink, M., Baud, O., Tanter, M., 2014. Ultrafast Doppler reveals the mapping of cerebral vascular resistivity in neonates. J. Cereb. Blood Flow Metab.

Ekroll, I.K., Dahl, T., Torp, H., Løvstakken, L., 2014. Combined vector velocity and spectral Doppler imaging for improved imaging of complex blood flow in the carotid arteries. Ultrasound Med. Biol. 40, 1629–1640.

Gesnik, M., Blaize, K., Deffieux, T., Gennisson, J.-L., Sahel, J.-A., Fink, M., Picaud, S., Tanter, M., 2017. 3D functional ultrasound imaging of the cerebral visual system in rodents. Neuroimage 149, 267–274.

Hansen, K.L., Møller-Sørensen, H., Kjaergaard, J., Jensen, M.B., Lund, J.T., Pedersen, M.M., Lange, T., Jensen, J.A., Nielsen, M.B., 2016. Intra-Operative Vector Flow Imaging Using Ultrasound of the Ascending Aorta among 40 Patients with Normal, Stenotic and Replaced Aortic Valves. Ultrasound Med. Biol. 42, 2414–2422.

Imbault, M., Chauvet, D., Gennisson, J.-L., Capelle, L., Tanter, M., 2017. Intraoperative Functional Ultrasound Imaging of Human Brain Activity. Sci. Rep. 7, 7304.

Leinenga, G., Langton, C., Nisbet, R., Götz, J., 2016. Ultrasound treatment of neurological diseases — current and emerging applications. Nat. Rev. Neurol. 12, 161–174.

Lenge, M., Ramalli, A., Tortoli, P., Cachard, C., Liebgott, H., 2015. Plane-wave transverse oscillation for high-frame-rate 2-D vector flow imaging. IEEE Trans. Ultrason. Ferroelectr. Freq. Control 62, 2126–2137.

Macé, E., Montaldo, G., Cohen, I., Baulac, M., Fink, M., Tanter, M., 2011. Functional ultrasound imaging of the brain. Nat. Methods 8, 662–664.

Maresca, D., Correia, M., Villemain, O., Bizé, A., Sambin, L., Tanter, M., Ghaleh, B., Pernot, M., 2017. Noninvasive Imaging of the Coronary Vasculature Using Ultrafast Ultrasound. JACC Cardiovasc. Imaging.

Montaldo, G., Tanter, M., Bercoff, J., Benech, N., Fink, M., 2009. Coherent plane-wave compounding for very high frame rate ultrasonography and transient elastography. IEEE Trans. Ultrason. Ferroelectr. Freq. Control 56, 489–506.

Osmanski, B.F., Martin, C., Montaldo, G., Lanièce, P., Pain, F., Tanter, M., Gurden, H., 2014. Functional ultrasound imaging reveals different odor-evoked patterns of vascular activity in the main olfactory bulb and the anterior piriform cortex. NeuroImage 95, 176–184.

Osmanski, B.-F., Pernot, M., Montaldo, G., Bel, A., Messas, E., Tanter, M., 2012. Ultrafast Doppler Imaging of Blood Flow Dynamics in the Myocardium. IEEE Trans. Med. Imaging 31, 1661–1668.

Osmanski, B.-F., Pezet, S., Ricobaraza, A., Lenkei, Z., Tanter, M., 2014. Functional ultrasound imaging of intrinsic connectivity in the living rat brain with high spatiotemporal resolution. Nat. Commun. 5, 5023.

Parikh, P., Juul, S.E., 2017. Neuroprotective Strategies in Neonatal Brain Injury. J. Pediatr. pii: S0022-3476(17)31091-0.

Pourcelot, L., 1976. Diagnostic Ultrasound for Cerebral Vascular Deseases, in: Present and Future in Diagnostic Ultrasound. Kooyker, p. 141.

Provost, J., Papadacci, C., Arango, J.E., Imbault, M., Fink, M., Gennisson, J.-L., Tanter, M., Pernot, M., 2014. 3D ultrafast ultrasound imaging in vivo. Phys. Med. Biol. 59, L1.

Qin, S., Caskey, C.F. & Ferrara, K.W., 2009. Ultrasound contrast microbubbles in imaging and therapy: physical principles and engineering. Phys. Med. Biol. 54, R27-57.

Rau, R., Scheffer, W., Belau, M., Kruizinga, P., De Jong, N., Bosch, J., Maret, G., 2017. 3D functional ultrasound imaging of the visual system in the pigeon brain. Presented at the 2017 IEEE International Ultrasonics Symposium (IUS).

Rideau Batista Novais, A., Pham, H., Van de Looij, Y., Bernal, M., Mairesse, J., Zana-Taieb, E., Colella, M., Jarreau, P.-H., Pansiot, J., Dumont, F., Sizonenko, S., Gressens, P., Charriaut-Marlangue, C., Tanter, M., Demene, C., Vaiman, D., Baud, O., 2016. Transcriptomic regulations in oligodendroglial and microglial cells related to brain damage following fetal growth restriction: FGR and the Developing Brain. Glia 64, 2306–2320.

Sandrin, L., Catheline, S., Tanter, M., Hennequin, X., Fink, M., 1999. Time-Resolved Pulsed Elastography with Ultrafast Ultrasonic Imaging. Ultrason. Imaging 21, 259–272.

Sandrin, L., Tanter, M., Catheline, S., Fink, M., 2002. Shear modulus imaging with 2-D transient elastography. IEEE Trans. Ultrason. Ferroelectr. Freq. Control 49, 426–435.

Sieu, L.-A., Bergel, A., Tiran, E., Deffieux, T., Pernot, M., Gennisson, J.-L., Tanter, M., Cohen, I., 2015. EEG and functional ultrasound imaging in mobile rats. Nat. Methods 12, 831–834.

Tanter, M., Bercoff, J., Athanasiou, A., Deffieux, T., Gennisson, J.-L., Montaldo, G., Muller, M., Tardivon, A., Fink, M., 2008. Quantitative Assessment of Breast Lesion Viscoelasticity: Initial Clinical Results Using Supersonic Shear Imaging. Ultrasound Med. Biol. 34, 1373–1386.

Urs, R., Ketterling, J.A., Silverman, R.H., 2016. Ultrafast Ultrasound Imaging of Ocular Anatomy and Blood Flow. Invest. Ophthalmol. Vis. Sci. 57, 3810–3816.

Van Raaij, M.E., Lindvere, L., Dorr, A., He, J., Sahota, B., Foster, F.S., Stefanovic, B., 2011. Functional micro-ultrasound imaging of rodent cerebral hemodynamics. NeuroImage 58, 100–108.