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● *Original Contribution*

ULTRASOUND MEASURES OF BRAIN PULSATILITY CORRELATE WITH SUBCORTICAL BRAIN VOLUMES IN HEALTHY YOUNG ADULTS

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Abstract—Increasing evidence suggests that brain pulsatility is involved in the pathophysiology of various neurological and psychiatric disorders. However, it remains unclear whether high brain pulsatility is damaging to or protective of the brain in normal conditions, and this could depend on the age of the individual and the methods used to measure brain pulsatility. The goal of our study was to investigate associations between subcortical volumes and brain pulsatility as assessed with ultrasound in healthy young adults using both a conventional method (transcranial Doppler pulsatility index [TCD-PI]) and the innovative method of tissue pulsatility imaging (TPI), which allows a high level of detection of small brain movements (micrometers). Twenty-five females aged 18–55 with no history of significant medical disorder underwent magnetic resonance imaging and ultrasound assessment. The volumes of six subcortical regions known to be particularly sensitive to change in cerebral blood flow were measured and compared with brain pulsatility as assessed with TCD-PI and TPI. TCD-PI and TPI measures positively correlated with all subcortical regions, with the caudate nucleus having the strongest association. Linear regressions found that TCD-PI and TPI measures of brain pulsatility explained 16% to 67% of the variance of the subcortical volumes. Our results suggest that a greater pulsatility as assessed with ultrasound in healthy young adults may constitute a protective factor for brain structure. Ultrasound measures of brain pulsatility may be appropriate to provide costless, non-invasive, portable and highly sensitive markers of cerebral blood flow pulsatility related to brain structure. (E-mail: t.desmidt@chu-tours.fr)

Key Words: **Brain pulsatility, Tissue pulsatility imaging, Transcranial Doppler, Brain volume.**

INTRODUCTION

How changes in intracranial pulsatility might affect normal and pathological brain structure is a question of recent interest, especially because an increasing number of studies tend to find associations between markers of intracranial pulsatility and brain-related disorders such as Alzheimer's disease and depression. It has been suggested that excessive intracranial pulsatility might damage the brain, as a consequence of intense and/or repetitive mechanical stress caused by pulsatile cerebral blood flow transmitted to the brain tissue (de Roos et al. 2017). On the contrary, other evidence suggests that greater pulsatility could be protective of the brain, especially because greater cerebral blood flow pulsatility has been found, in some experiments, to decrease neural damage and because greater pulsatile cerebral blood flow (CBF) can result in greater mean flow rates (Rickards and Tzeng 2014). Whether brain pulsatility is protective or deleterious could depend on the age of the individual. Indeed, most of the studies finding a negative impact of intracranial pulsatility involve older adults whose cerebrovascular system may exhibit impairment, including arterial stiffening, which is a factor of increased intracranial pulsatility. In contrast, in healthy young adults, a greater brain pulsatility and greater cerebral blood flow may be neuroprotective. However, although some studies have investigated associations between intracranial pulsatility and brain changes in

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older adults, little is known about the effect of intracranial pulsatility on brain structure in young adults.

Ultrasound methods can be used to characterize markers of intracranial pulsatility and include the conventional transcranial Doppler (TCD) and the recently developed tissue pulsatility imaging (TPI). TCD allows the measurement of cerebral blood flow velocity, from which the pulsatility index (PI) can be calculated as a marker of the amplitude of arterial pulsatility. More recently, advances in ultrasound imaging, both in probe technology and in signal processing, have made possible the development of TPI, which is similar to TCD, except that rather focusing on only large arteries, it relies on the Echo-B mode of a modern ultrasound scanner to measure the pulsatile movements of large brain regions and allows a very high spatiotemporal level of detection (micrometers/millisecond) of brain volume changes related to pulsatile CBF. TPI has been validated on phantoms (Kucewicz et al. 2004) and on healthy volunteers during visual stimulation (Kucewicz et al. 2007) and hyperventilation (Kucewicz et al. 2008), which suggests that brain tissue pulsatility (BTP) is closely related to CBF changes and cerebrovascular reactivity. Our team also found that TPI was informative in clinical settings, as BTP was reported to be inversely correlated with white matter hyperintensity load (Ternifi et al. 2014) and was changed in depression (Desmidt et al. 2011, 2017) and in older adults with orthostatic hypotension (Biogeau et al. 2017).

The goal of our study was to investigate associations between brain volume and brain pulsatility as assessed with TCD-PI and TPI in healthy young and middle-aged individuals. We chose to focus on subcortical regions because subcortical nuclei are particularly sensitive to change in CBF (Moody et al. 1990), as they are in the range of the ultrasound assessment and they have been found to be associated with pulsatility in older adults.

METHODS

Participants

Twenty-five females aged 18 to 55 y were recruited from the local community and from the records of the research center of the Hospital of Tours, France. Participants in this study were healthy controls from the EMPHILINE Project (NCT02026622 on clinicaltrials.gov), the principal objective of which was to investigate cardiovascular and cerebrovascular reactivity in depression during emotional tasks; the baseline data are reported in this article. To reduce variability, only females were recruited because previous findings have found significant differences in cerebrovascular properties between age-matched males and females (Parkes et al. 2004). They had to have no current or history of any significant medical and psychiatric disorders. Non-inclusion criteria were (i) any history of psychotic, bipolar, or substance-abuse disorders or suspicion of severe cognitive impairment (MMSE <25); (ii) any history of severe cardiovascular diseases (myocardial infarction, arrhythmia, *etc.*) or neurological disorders (stroke, brain tumor, severe concussion, migraine, *etc.*); (iii) any current unstable medical condition; (iv) current use of beta blockers or antipsychotics; (v) smoking more than 10 packs a year; (vi) auditory or visual impairments; (vii) pregnancy or no reliable contraception; (viii) contraindication to magnetic resonance imaging; and (ix) legal guardianship. The exclusion criterion was having no temporal window because US is attenuated by the thickness of the skull. Informed consent was obtained from all participants included in the study, and the study protocol was approved by the local human ethics committee.

Clinical assessments

Either a psychiatrist (T.D.) or a trained medical doctor (V.G.) from the research center performed the clinical assessments in the research center of the University Hospital of Tours, France. Medical history and medication intake were recorded. The clinical assessment included blood pressure (measured immediately before the US assessment), height and weight measurements.

Magnetic resonance imaging protocol

Magnetic resonance imaging (MRI) scanning sessions were performed immediately after the psychometric assessment on a 3-T Siemens Verio scanner (Siemens AG, Erlangen, Germany). A high-resolution T1-weighted MRI 3-D volume sequence (192 contiguous sagittal slices; 1-mm slice thickness; TR = 1.9 s; TE = 2.42 ms; TI = 0.9 ms; FA = 9°; in-plane resolution: 1 × 1 mm) was acquired for each subject. Additional sequences (T2-weighted and fluid-attenuated inversion recuperation) were acquired and analyzed to rule out concomitant diseases such as ischemic stroke and susceptibility artifacts from prior hemorrhage or space-occupying lesions. Severe white matter lesion load was used as an exclusion criterion.

Structural image processing

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Fischl et al. 2002, 2004a, 2004b; Reuter et al. 2010; Ségonne et al. 2004). Briefly, this processing includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne