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Structural properties of the human corpus callosum: Multimodal assessment and sex differences

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ABSTRACT

A number of structural properties of white matter can be assessed *in vivo* using multimodal magnetic resonance imaging (MRI). We measured profiles of R1 and R2 relaxation rates, myelin water fraction (MWF) and diffusion tensor measures (fractional anisotropy [FA], mean diffusivity [MD]) across the mid-sagittal section of the corpus callosum in two samples of young individuals. In Part 1, we compared histology-derived axon diameter (Aboitiz et al., 1992) to MRI measures obtained in 402 young men (19.55 ± 0.84 years) recruited from the Avon Longitudinal Study on Parents and Children. In Part 2, we examined sex differences in FA, MD and magnetization transfer ratio (MTR) across the corpus callosum in 433 young (26.50 ± 0.51 years) men and women recruited from the Northern Finland Birth Cohort 1986. We found that R1, R2, and MWF follow the anterior-to-posterior profile of small-axon density. Sex differences in mean MTR were similar across the corpus callosum (males > females) while these in FA differed by the callosal segment (Body: M > F; Splenium: F > M). We suggest that the values of R1, R2 and MWF are driven by high surface area of myelin in regions with high density of "small axons".

Introduction

Corpus callosum (CC) is the main interhemispheric fiber tract in the human brain, consisting of about 200 million axons (Aboitiz et al., 1992). Heterogeneity of its fiber composition, as seen in the variation in density of small and large fibers along the anterior-posterior axis, suggests that cortical regions differ in the type of channels carrying information between their left-right homologues (Aboitiz and Montiel, 2003; De Lacoste et al., 1985). In the developing (monkey) brain, over 4 million callosal axons are lost per day during the first 3 post-natal weeks, with 70% of callosal axons lost during the first 3 post-natal months (LaMantia and Rakic, 1990). Later in life, the absolute number of axons does not change but the proportion of large myelinated callosal fibers appears to increase (Aboitiz et al., 1996). In humans, age-related changes in the corpus callosum have been studied using magnetic resonance imaging (MRI), which revealed nonlinear heterochronous developmental trajectories in callosal segments (Giedd et al., 1999; Tanaka-Arakawa et al., 2015). A number of diseases are associated with abnormalities in white matter (WM), including the corpus callosum (Filippi and Cauley, 2014; Renard et al., 2014). This is the case for brain disorders such as multiple sclerosis (Garg et al., 2015; Bachman et al., 2014), Alzheimer's disease (Bachman et al., 2014; Walterfang et al., 2014) and schizophrenia (Innocenti et al., 2003; Wheeler and Voineskos, 2014).

Magnetic resonance imaging allows one to assess various structural properties of the corpus callosum, including its size (Luders et al., 2014; Scamvougeras et al., 2003), shape (Bachman et al., 2014; Prendergast et al., 2015) and microstructure (Hofer and Frahm,

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2006). Each voxel represents a composite of axons, myelin and extracellular space. This cellular environment can be characterized using quantitative MRI (qMRI) methods. A combination of qMRI data with the knowledge of the underlying histology and the biophysical description of the MR contrast-generating parameters enables reverse modeling of WM microstructure *in vivo*, for a review see (Weiskopf et al., 2015). Different cellular features are invoked when interpreting data acquired with different MRI modalities. *Diffusion tensor imaging* (DTI) maps the microstructure of diffusion barriers, including those created by axons, with metrics such as fractional anisotropy (FA) and mean diffusivity (MD) (Masutani et al., 2003; Mori and Zhang, 2006; Papadakis et al., 1999; Basser et al., 1994; Pierpaoli and Basser, 1996), *magnetization transfer ratio* (MTR) appears to scale with the amount of macromolecules, including myelin (Grossman et al., 1994; Henkelman et al., 2001; Hickman et al., 2004; Kucharczyk et al., 1994; Lexa et al., 1994; Schmierer et al., 2004), *myelin water fraction (MWF)* and *longitudinal* (R1) and *transverse* (R2) *relaxation rates* represent markers for water content and myelin (Clark et al., 1992; Dyakin et al., 2010; Laule et al., 2006; Lutti et al., 2014).

Histological information derived from postmortem studies is crucial for making inferences from qMRI findings and for creating biophysical models of WM tissue. Histology of corpus callosum is well characterized in human (Caminiti et al., 2013; Aboitiz et al., 1992; Witelson et al., 2006) and non-human (He et al., 2007; Juraska and Kopcik, 1988; LaMantia and Rakic, 1990; Stikov et al., 2015a) primates. One of the features capturing the relationship between axon diameter and myelin thickness is the g-ratio. It is calculated as the division of the inner (without myelin) by the outer (with myelin) diameter of a myelinated axon; g ratio serves as a parameter of relative myelin thickness with an approximate optimal value of 0.6 (Rushton, 1951; Thomas and Ochoa, 1984). G-ratio is one example of models of tissue microstructure that can be estimated from qMRI data (Stikov et al., 2015b; West et al., 2015). We have argued that both myelin thickness and axon diameter should be considered simultaneously when interpreting variations in WM observed during development, aging and in relation to psychopathology (Paus et al., 2014; Paus, 2010; Paus and Toro, 2009).

The focus of this study is on the microstructure of the corpus callosum (CC), a tract with minimal fiber crossings and well-documented histology. In Part 1, we combine information from five MRI-based measures (FA, MD, R1, R2 and MWF) obtained in a sample of 402 young men (recruited from the Avon Longitudinal Study of Parents and Children) with earlier literature on CC histology. In Part 2, we use this knowledge to interpret sex differences in MRI-based properties of the CC observed in a total of 433 young men and women (recruited from the Northern Finland Birth Cohort 1986). Based on previous studies, we hypothesize that higher FA (Westerhausen et al., 2004) and lower MTR (Perrin et al., 2009) values are present in the male vs. female corpus callosum.

Materials and methods

Study setting

Part 1

Multimodal MRI of 402 young men from the Avon Longitudinal Study of Parents and Children (ALSPAC: http://www.alspac.bris.ac.uk) and histological data from Aboitiz et al. Aboitiz et al., (1992) were included to characterize the relationship between *in vivo* and *ex vivo* structural properties of the CC.

Participants. The Avon Longitudinal Study of Parents and Children birth cohort was designed to investigate the influence of various factors on health trajectories. Pregnant women residing in the former Avon Health Authority in South-West England, who had an estimated date of delivery between 1 April 1991 and 31 December 1992 were invited to participate in the study. This resulted in a cohort of 14,541 pregnancies, of which 13,988 singletons/twins were alive at 12 months of age (Boyd et al., 2013; Fraser et al., 2013). The study is still engaged with over 11,000 participants who have been tested multiple times during their infancy, childhood and adolescence and are eligible for future follow up. Ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

Subsample with brain MRI data. A total of 507 male participants from ALSPAC were scanned. Only male participants were included owing to the focus of the NIH grant funding this work. Participants were selected based on their current domicile being within a 3- hour journey (1-way) from the scanning site and the availability of a minimum of three blood samples obtained for sex hormone assays (Khairullah et al., 2014). The sample included the first 507 participants who met these criteria and accepted the invitation to take part in the MRI substudy. Of these 507 participants, 456 completed all scanning using an identical protocol (i.e., structural R1, R2, MWF, MTR and DTI). From this sample, we excluded participants with partly missing or corrupt data (26 participants) or extreme outliers (defined as ± 4 SD) on any of the WM measures (28 participants), leaving 402 participants (age 18 to 21 years, mean [SD] = 19.55 [0.84]).

Aboitiz histological dataset. Histological data were acquired by Aboitiz et al. (1992). Mean axon densities and standard deviations for the 10 CC segments were calculated from data provided for this study by Dr. Franscisco Aboitiz (Personal communication, August 31, 2015). Aboitiz et al. present densities for four classes of axon diameter, of which the two extremes ("small" fibers: > 0.4 μm [D04]; "large" fibers: > 5 μm [D5]) were chosen to account for most of the density variations in CC.

Part 2

Participants. The Northern Finland Birth Cohort 1986 study (NFBC 1986; http://www.oulu.fi/nfbc/) is a prospective population-based collection of health-related information about individuals with expected date of birth between the 1st of July 1985 and the 30th of June 1986 in the two northernmost provinces of Finland. A total of 9362 deliveries, i.e. 99% of all deliveries in the target period, were recorded (Järvelin et al., 1993). Data for the whole NFBC 1986 have been gathered from the mothers during pregnancy and from the offspring at the 7–8 years and 15–16 years follow-ups. Also information of the offspring's somatic and psychiatric illness has been obtained from the Care Register for Health Care.

Subsample with brain MRI data. Of the original sample, 6985 (74%) participated in the 16-year follow-up. Among this group, there were 698 individuals exposed to smoking during pregnancy and eligible for inclusion after consideration of inclusion and exclusion criteria as described in Lotfipour et al. (2014). The non-exposed control group was selected randomly from offspring of non-smoking mothers with the same inclusion and exclusion criteria. Non-exposed controls were matched to the exposed participants by place of birth and maternal education.

Of the invited 1396 eligible participants (698 exposed and 698 matched non-exposed), a total of 471 (34%) participated the MRI study. Scanning was completed successfully in 451 participants. Common contraindications for the MRI acquisition included pregnancy, participant's metal or electronic implants and severe claustro-