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White matter alterations at pubertal onset

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ABSTRACT

Recent neurodevelopmental research supports the contribution of pubertal stage to local and global grey and white matter remodelling. Little is known, however, about white matter microstructural alterations at pubertal onset. This study investigated differences in white matter properties between pre-pubertal and pubertal children using whole brain fixel-based analysis (FBA) of the microscopic density and macroscopic cross-section of fibre bundles. Diffusion-weighted imaging data were acquired for 74 typically developing children (M=10.4, SD=.43 years, 31 female) at 3.0 T (60 diffusion gradient directions, b-value=2800 s/mm^2). Group comparisons of fibre density (FD) and fibre cross-section (FC) were made between age-matched pre-pubertal and pubertal groups, and post-hoc analyses were performed on regions of interest (ROIs) defined in the splenium, body and genu of the corpus callosum. Significant fixel-wise differences in FD were observed between the pubertal groups, where the pubertal group had significantly higher FD compared with age-matched pre-pubertal children, localised to the posterior corpus callosum. Post-hoc analyses on mean FD in the corpus callosum ROIs revealed group differences between the pubertal groups in the splenium, but not body or genu. The observed higher apparent fibre density in the splenium suggests that pubertal onset coincides with white matter differences explained by increasing axon diameter. This may be an important effect to account for over pubertal development, particularly for group studies where age-matched clinical and typical populations may be at various stages of puberty.

Introduction

Puberty is a critical period of development, marking the transition from childhood to reproductive maturity (Dorn et al., 2006). Adrenarche describes the earliest phase of puberty, beginning between the ages of 6 – 9 in females, and approximately 1 year later in males (Grumbach and Styne, 1998). It is the period in which physical changes begin to manifest. Endocrine events tied to puberty such as activation of the hypothalamic-pituitary-adrenal (HPA) and -gonadal (HPG) axes leads to increased production of adrenal and gonadal steroid hormones, which have been shown to enter the blood brain barrier and initiate remodelling of the brain in animal models (Sisk and Foster, 2004).

Quantifying these hormone levels in puberty, however, is inherently limited by individual variability and diurnal pattern of hormone concentrations, making it difficult to infer pubertal stage (Ankarberg and Norjavaara, 1999). The Pubertal Development Scale (PDS) is a non-invasive self or parent-report measure of pubertal stage that is highly correlated with hormones and physical exam (Shirtcliff et al., 2009).

A growing body of evidence suggests that the timing of pubertal onset can lead to differential patterns of grey and white matter development evidenced by Magnetic Resonance Imaging (MRI) (Blakemore et al., 2010; Byrne et al., 2016; Ladouceur et al., 2012). In the context of grey matter, there is converging evidence of a positive relationship between pubertal stage and pituitary volume (Whittle

Abbreviations: BMI, body mass index; CFE, connectivity-based fixel enhancement; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FA, fractional anisotropy; FBA, fixel-based analysis; FC, fibre cross-section; FD, fibre density; FDC, fibre density and cross-section; FOD, fibre orientation distribution; FWE, family-wise error; GLM, general linear model; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; JHU, John's Hopkins University; MRI, magnetic resonance imaging; PDS, pubertal development scale; SEIFA, socio-economic indexes for areas; SES, socio-economic status; TE, echo-time; TR, repetition time; WASI, Wechsler abbreviated scale of intelligence

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et al., 2012; Wong et al., 2014), global grey matter density (Peper et al., 2009), and amygdala volume (Goddings et al., 2014; Neufang et al., 2009).

In addition to physical indices of pubertal maturation, endogenous adrenal and sex steroid hormone levels have been associated with grey and white matter structure. In early puberty, corpus callosum body volume is higher with increased luteinizing hormone (LH) levels (Peper et al., 2008). Testosterone levels are associated with increased white matter volume (Perrin et al., 2008), as well as sex-dependent relationships in grey matter surface area (Herting et al., 2015) and corticospinal structure (Pangelinan et al., 2016).

Diffusion MRI techniques have allowed the in-vivo quantification of properties of white matter microstructure during this dynamic period of brain development. A number of diffusion tensor imaging (DTI) studies have revealed greater microstructural organisation with pubertal advancement (Asato et al., 2010; Herting et al., 2012; Menzies et al., 2015). Whilst DTI is the most commonly used technique to assess white matter microstructure, metrics such as fractional anisotropy (FA) are non-specific at distinguishing between white matter properties such as axon density, myelination, glial infiltration, crossing fibres, and partial voluming. These are all separate physio-anatomical properties of white matter that must be disentangled to fully understand the nature of white matter changes across development (Beaulieu, 2009).

Since chronological age and pubertal stage are highly correlated, highly sensitive as well as specific models that interrogate white matter microstructure at the fibre level are necessary to disentangle 'pubertal age', or pubertal contributions to white matter microstructure, from chronological age. Despite these advancements, disentangling age-related mechanisms of brain development from pubertal processes remains a challenge.

Recent advances have introduced more specific measures of axon density and fibre bundle cross-section (Groeschel et al., 2016). Neurite density index from NODDI (Zhang et al., 2012) can characterise the density of neurites by restricted diffusion by modelling the intracellular space (Sepehrband et al., 2015). Whilst more sensitive than DTI metrics to age-related differences in the developing brain (Genc et al., 2017), there has been some debate regarding its interpretation in areas in multiple crossing fibres, and the underlying assumptions of the model (Lampinen et al., 2017; Novikov et al., 2016).

Fixel-based analysis (FBA) (Raffelt et al., 2012, 2017) is a recently developed diffusion MRI analysis technique that uses fibre-population specific information to estimate fibre density and morphology for individual white matter fibre populations. A *fixel* is defined as a *fi*bre-population within a vo*xel*, and as such FBA allows for whole-brain comparisons of fibre-specific white matter properties. It produces metrics that assess fibre density (FD), fibre cross-section (FC), and the combined effect of fibre density and cross-section (FDC), where FD for a given fibre population is proportional to the volume of the intra-axonal compartment. FC reflects the cross-sectional area of the white matter fibre bundle, and FDC reflects the combined effect of FD and FC. Increases in FD can represent an increase in axonal count, or denser packing of axons, in a given fibre area, whereas increases in FC can suggest greater cross-sectional area of a fibre bundle.

In this study, we implement fixel-based analysis to estimate and compare white matter fibre density and morphology across two age-matched groups of children: pre-pubertal (no evidence of maturation of secondary sexual characteristics), and pubertal (evidence of pubertal maturation).

Methods

Participants

This paper reports on a subsample of typically developing children recruited as part of the Neuroimaging of the Children's Attention Project study (see Silk et al. (2016) for a detailed protocol). Briefly, children were recruited from 43 socio-economically diverse primary schools distributed across the Melbourne metropolitan area, Victoria, Australia. MR imaging was performed on 86 typically developing children. Of those, 8 participants were excluded owing to missing or motion-affected diffusion MRI data, and a further 4 participants were excluded owing to missing pubertal data, resulting in a total of 74 children aged 9.5–11.9 years being included in the current study. This study was approved by The Royal Children's Hospital Melbourne Human Research Ethics Committee (HREC #34071).

As part of the assessment procedure, a number of participant characteristics were determined based on child and parent report. Socio-economic status (SES) was determined using the Socio-Economic Indexes for Areas (SEIFA). General intellectual ability was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI) matrix reasoning sub-test (Wechsler, 1999). Height and weight were measured using the average of two consecutive measurements to calculate a Body-Mass index (BMI) (kg/m^2). Participant characteristics are summarised in Table 1.

Pubertal classification

Pubertal development was assessed using the Pubertal Development Scale (PDS) (Petersen et al., 1988). The PDS is a measure that assesses pubertal stage and is highly correlated with hormonal measures and physical exam by a trained physician, rendering it a reliable measure of pubertal maturation (Shirtcliff et al., 2009). For the current study, the primary caregiver was asked to rate their child's physical development on a four-point scale. This included questions assessing the presence of characteristics phenotypical of pubertal onset such as deepening of voice and presence of facial hair in boys, and breast development and menarche for females. A combined PDS-Shirtcliff (PDSS) score was calculated (Shirtcliff et al., 2009) by taking the mean of the adrenarche and gonadarche scores generated from the syntax described in the aforementioned study. The PDSS scores in our sample ranged from 1 to 3.5, where children with a score of 1 had no physical signs of pubertal onset, and children with a score of 1.5–3.5 had some phenotypic characteristics of pubertal onset. Subsequently, the sample was divided into two groups: *pre-pubertal* (children with PDSS =1) and *early-pubertal* (children with PDSS ≥1.5). For ease of explanation, the early-pubertal group (PDSS ≥1.5) will be referred to as the *pubertal* group.

Image acquisition and processing

Diffusion-weighted imaging (DWI) data were acquired on a research-dedicated 3.0 T Siemens Tim Trio MRI scanner (Erlangen, Germany) at The Melbourne Children's campus, Melbourne,

Table 1
Demographics and participant characteristics by pubertal group. Values reported as M (SD) unless otherwise stated.

	Pre-pubertal *(n=44)*	Pubertal *(n=30)*	Group difference *p-value*
Age (years)	10.41 (.40)	10.45 (.48)	.71[a]
Sex, *n(% male)*	31 (68)	12 (40)	< .01[b*]
Handedness, *n(% right)*	35 (80)	27 (90)	.23[b]
Body Mass Index (BMI)	17.96 (3.03)	19.20 (3.12)	.09[a]
Socio-economic status (SES)	1032 (41)	1005 (56)	.56[a]
WASI matrix reasoning (T-score)	51.70 (7.64)	54.77 (6.39)	.08[a]

M, mean; SD, standard deviation; WASI, Wechsler Abbreviated Scale of Intelligence. Difference between pre-pubertal and pubertal groups defined using:
[a] independent samples *t*-test;
[b] Chi-square test.
[*] Denotes a significant group difference.