NeuroImage: Clinical 24 (2019) 101980

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

White matter microstructural abnormalities in children with severe congenital hypothyroidism

Hannah E. Cooper[a,g,*,1], Enrico Kaden[b], Lorna F. Halliday[c], Doris-Eva Bamiou[d,h], Kshitij Mankad[e], Catherine Peters[f], Christopher A. Clark[a]

[a] Developmental Imaging and Biophysics Section, UCL Great Ormond Street Institute of Child Health, London, UK
[b] Centre for Medical Image Computing, Department of Computer Science, University College London, London, UK
[c] MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK
[d] UCL Ear Institute, Faculty of Brain Sciences, University College London, London, UK
[e] Department of Neuroradiology, Great Ormond Street Hospital for Children, London, UK
[f] Department of Endocrinology, Great Ormond Street Hospital for Children, London, UK
[g] Royal Berkshire NHS Foundation Trust, Reading, UK
[h] National Institute of Health Research (NIHR), University College London Hospitals Biomedical Research Centre, London, UK

ARTICLE INFO

Keywords:
Communication
Diffusion tensor imaging
Endocrine
Hearing
MRI

ABSTRACT

This study assessed white matter microstructural integrity and behavioral correlates for children with severe congenital hypothyroidism (CH) who were identified and treated early following newborn screening. Eighteen children with severe CH and 21 healthy controls underwent a battery of behavioral measures of hearing, language and communication, along with diffusion MR imaging. Tract-based spatial statistics were performed on standard diffusion parameters of fractional anisotropy and diffusivity metrics. Microscopic diffusion anisotropy mapping based on the Spherical Mean Technique was also used to evaluate biologically specific metrics. Compared with age-matched controls, children with severe CH had poorer hearing and communication skills, albeit generally within normal limits. Children with severe CH had fractional anisotropy that was significantly lower in the cerebellum, bilateral thalami and right temporal lobe, and radial diffusivity that was significantly higher in the cerebellum and bilateral thalami. Microscopic fractional anisotropy and intra-neurite volume fraction were also significantly decreased, and transverse microscopic diffusivity was significantly increased, in the CH group in areas including the cerebellum, thalamus, occipital lobe, and corpus callosum, and in the white matter adjacent to sensorimotor cortex, particularly in the left hemisphere. Significant and widespread correlations were observed between behavioral measures and measures of white matter microstructural integrity in children with CH. The results indicate that children with severe CH who are identified through newborn screening may have significant brain white matter microstructural abnormalities despite early treatment.

1. Introduction

Congenital hypothyroidism (CH) affects around 1 in every 3000–4000 live births (Fisher, 1983) and is defined as thyroid hormone deficiency that is present at birth. Thyroid hormone is essential for the development of normal neuronal networks, and untreated CH causes severe, permanent alterations in the anatomy and function of the brain macro- and microstructure (Prezioso et al., 2018), leading to severe growth retardation and learning disabilities. CH is, however, one of the most treatable causes of intellectual and physical impairment, and universal newborn screening programs are in place in many developed countries (Bernal and Nunez, 1995; Donaldson and Jones, 2013; Hulse, 1984; Rastogi and LaFranchi, 2010). Early treatment has greatly improved outcomes for children with CH, with severe problems being virtually eliminated where screening programs exist. However, infants with CH still experience a period of thyroid hormone insufficiency, and are therefore at risk of neurodevelopmental deficits (Rovet, 1999a, 1999b).

The incidence of CH varies by geographic location due to factors including iodine status as well as variation in incidence between different racial and ethnic groups (Rastogi and LaFranchi, 2010). A higher incidence is reported in females who usually outnumber males by factor

* Corresponding author.
E-mail address: hannah.cooper@ucl.ac.uk (H.E. Cooper).
[1] Present address: UCL Ear Institute, Faculty of Brain Sciences, University College London, London, UK.

https://doi.org/10.1016/j.nicl.2019.101980
Received 22 September 2018; Received in revised form 29 July 2019; Accepted 8 August 2019
Available online 10 August 2019

of two (Alm et al., 1984). Several countries have seen increasing incidence of CH since screening began. This rise has been attributed to increased sensitivity of testing strategy resulting in milder cases being detected (Donaldson and Jones, 2013; Mitchell et al., 2011; Rastogi and LaFranchi, 2010). There is also evidence from a Japanese study that maternal exposure to environmental pollutants may be related to the increase in incidence (Nagayama et al., 2007).

Newborn screening programs vary by geographic location. However, in the UK, all newborns are offered blood spot screening on or around day 5, and infants whose levels of thyroid stimulating hormone (TSH) are ≥10 mU/L are referred to pediatric endocrinology on the same or the next working day (Griffiths et al., 2014). Diagnostic measurement of thyroxine (T4) and TSH blood levels is then undertaken and, should CH be confirmed by a low T4 (or free T4), treatment with levothyroxine, a synthetic form of T4, is implemented as soon as possible in order to restore T4 and TSH to the normal range. In the UK, current guidelines recommend that treatment be commenced within 17 days of birth (Knowles, 2011) and that normalization of TSH be achieved within one month of treatment initiation (Griffiths et al., 2014; S. I. Song et al., 2001). Treatment is continued for life, unless the condition is transient, in order to maintain biochemical and clinical euthyroidism. Careful clinical monitoring needs to be undertaken in order to ensure that patients on high dose levothyroxine are not overtreated, with one study proposing that this leads to temperamental difficulties in infants (Rovet et al., 1989), and another showing adverse effects on cognitive development at 11 years (Bongers-Schokking et al., 2013). However, a further study showed no adverse effects of high starting dose of levothyroxine on behavioral outcomes such as memory, attention or behavior at 20 years (Oerbeck et al., 2005). Age of treatment onset and severity of CH both affect neurocognitive outcome, with earlier treatment initiation and milder disease being associated with better outcomes (Rastogi and LaFranchi, 2010).

Animal models have shown various effects of early thyroid deficiency on the developing brain. Neonatal hypothyroidism in rats (corresponding to a human fetus in the second trimester of pregnancy) has been shown to affect cell migration and branching in the cerebellum, leading to delays in cell migration and a substantial reduction in Purkinje cell differentiation (Bernal, 2002). Moreover, synapse formation has been shown to be adversely affected, again most prominently in the Purkinje cells of the cerebellum which show substantially reduced dendritic branching (Bernal, 2002). Oligodendrocyte and astrocyte density is finely controlled by thyroid hormone concentrations, and major white matter tracts such as the corpus callosum and anterior commissure show imbalance in these two cell types in animal models of CH (Sharlin et al., 2008). Myelination is also affected in the neonatal hypothyroid rat brain, with delayed and reduced deposition of myelin, leading to a reduction in the final number of myelinated axons compared with healthy animals (Balazs et al., 1969).

In humans, neuroimaging techniques can be used to assess brain development following CH. Such studies have revealed that infants and children with a broad range of diagnostic CH (including transient and ectopic CH) are not at a greater risk of gross structural abnormalities on conventional MRI (Rachmiel et al., 2013; Siragusa et al., 1997). However, children with various thyroid defects (including agenesis and ectopic thyroid gland, dyshormonogenesis with equivocal screening results, and those diagnosed clinically rather than via screening) showed reduced hippocampal size compared with healthy controls (Wheeler et al., 2011). Cortical morphology studies have shown various areas of cortical thinning and thickening in children with CH compared with typically developing controls, and significant correlations have been shown between cortical thickness and concentrations of free T4 (fT4) and TSH at diagnosis (Clairman et al., 2015). Finally, children with CH have been shown to demonstrate abnormalities in hippocampal functioning during memory tasks (Wheeler et al., 2015; Wheeler et al., 2011), and in activation of the somatosensory and parietal cortices during visuospatial processing (Blasi et al., 2009). Hippocampal functioning was found to be related to severity of CH in early life (Wheeler et al., 2011).

Aside from neuroimaging, studies have also identified behavioral consequences of CH. Such studies suggest that, despite early treatment, 10–25% of children with CH will be diagnosed with a mild or mild-moderate hearing loss, approximately half of whom have a sensorineural hearing loss and half a conductive loss (Bruno et al., 2015; Lichtenberger-Geslin et al., 2013; Rovet et al., 1996). Moreover, a previous report has identified possible abnormalities in auditory electrophysiological measures, suggesting alterations at the level of the auditory cortex following CH (Oerbeck et al., 2007). Children with CH may present with delayed language, particularly those with thyroid agenesis or complete dyshormonogenesis (Alvarez et al., 2004; Bargagna et al., 2000; S. I. Song et al., 2001), and those with additional sensorineural hearing loss have been shown to have poorer expressive and receptive language scores than those with CH who have normal hearing thresholds (Rovet et al., 1996). However, there may be an effect of age, in that the language development of younger children diagnosed and treated early with CH is delayed, but then progresses until they attain comparable levels to their peers (Bargagna et al., 2000).

1.1. The current study

The literature therefore suggests that children with CH who were treated early may nonetheless be at greater risk of subtle changes in myelination, as well as hearing loss, memory and visual-spatial difficulties, and difficulties with language development relative to their typically developing peers. However, previous neuroimaging studies have evaluated broad, heterogeneous groups of children including those with transient and ectopic CH, and thyroid dysgenesis (complete or partial failure of maturation and migration of the developing thyroid to the correct anatomical position in the neck resulting in agenesis or ectopia of the thyroid) as well as late-identified children. Moreover, as yet, no studies have examined white matter pathways in children with CH. The current study aims to address these shortcomings, by examining the white matter integrity, hearing, cognitive, and language profiles of children with severe CH (i.e., those with undetectable concentrations of fT4 (< 3.9 pmol/l) and TSH > 375 mU/l at birth). These children are at the greatest risk of poor outcomes (Bargagna et al., 2000; Rovet, 2014). While recent studies have suggested that this risk may be reduced by giving high dose initial thyroid hormone replacement therapy (Albert et al., 2013; Aleksander et al., 2018), this comes with its own risk of behavioral and psychological issues in children and adolescents (Kopp et al., 1995; Rovet and Ehrlich, 1995; Rovet et al., 1989).

Advanced diffusion MRI (multishell diffusion MRI) was used to investigate white matter microstructure in children with CH. Quantitative neuroimaging can be used to examine microstructural integrity of the developing human brain in vivo. Diffusion tensor imaging (DTI; Basser and Pierpaoli, 1996) provides the fractional anisotropy (FA) which relates to the coherence of white matter bundles and mean diffusivity (MD) which reflects the microstructural density of brain tissue. Even though DTI has been widely used for the assessment of tissue microstructure, it is well known that this technique conflates orientation and microstructural effects. Specifically, DTI-based anisotropy indices do not only depend on microscopic tissue features, such as the grade of myelination and neurite density, but are confounded by fiber crossings and orientation dispersion, which are ubiquitous in the brain (Schmahmann et al., 2007).

More recently, a new class of diffusion MRI techniques has emerged - *microscopic diffusion anisotropy imaging* - that factors out the confounding effects of the intra-voxel fiber orientation distribution. This technique therefore provides a direct estimate of microscopic tissue structure. A clinically viable approach is the Spherical Mean Technique (SMT), which requires a diffusion sequence with two b-shells achievable within practical scan time (Kaden et al., 2016b). The key insight of

this technique is that for any fixed gradient magnitude and timing, i.e. fixed b-value, the spherical mean of the diffusion signal over the gradient directions does not depend on the directional tissue structure.

The study hypotheses are that:

1. Children and adolescents with severe CH show reductions in the density of white matter pathways compared with age-matched controls;
2. Children and adolescents with severe CH show deficits in hearing, cognition, communication, and language compared with age-matched controls; and
3. White matter microstructure as measured by diffusion metrics correlate with clinical scores, including early TSH concentrations, hearing, cognition, communication, and language for children and adolescents with severe CH.

2. Materials and methods

2.1. Participants

Participants with severe CH were recruited from the Department of Endocrinology at Great Ormond Street Hospital (GOSH) and all had been diagnosed through the NHS Newborn Blood Spot Screening Programme. Typically developing controls were recruited via advertisements to staff at GOSH and UCL. Staff were sent a brief email outlining the study including the entry criteria, and asking them to contact the study team if they had a child or children who may be interested in taking part.

The study was limited to children aged 6 years and over as rapid changes in myelination occur prior to this point (Schmithorst et al., 2005). Those with any contraindications to MRI scanning, middle ear disease present at the time of testing or any progressive neurological condition were excluded. Controls were additionally excluded if they had any current hearing, language or communication problems, or any history of thyroid disease. The study was approved by the Joint Research Ethics committee of GOSH/UCL Institute of Child Health and written informed consent was given by participants' parents with assent/consent from the participants themselves as appropriate. Postcode data were used to measure socioeconomic status via the Index of Multiple Deprivation (Noble et al., 2007).

Eighteen children with severe CH (11 female, mean age = 9.67 ± 2.19 years, age range 6.24 to 15.44 years) and 21 controls (11 female, age = 10.34 ± 2.98 years, age range 7.26 to 16.06) participated in the study. One control participant was found to have evidence of middle ear effusion and a conductive hearing loss at the time of testing and was excluded from the rest of the study. One participant with CH also had a diagnosis of autism spectrum disorder and was unable to complete the majority of the language assessment; his results were therefore excluded. This left 17 participants with CH and 20 controls for this part of the study. A CONSORT flow diagram showing recruitment and exclusions at each stage of the study is shown in Supplementary Fig. 1.

2.1.1. Historical thyroid function assessment

Bloodspot TSH concentrations were measured by the automated dissociation enhanced lanthanide fluoro immuno assay (AutoDELFIA, Perkin Elmer, United Kingdom) system. This method is calibrated using six standards with values ranging from < 1 mU/l to 300 mU/l with some variation for each kit lot. The interbatch precision of this method ranges from 6% to 8% with no trend over the range of values. TSH in dried bloodspot specimens has been shown to be stable for at least 1 month at room temperature. If stored at + 4 °C with desiccant, there is no degradation of TSH for at least 1 year. All samples in this study were analyzed within 1 month of sample collection. There was no modification or change to the assay procedure during the study period and no assay drift was reported. The assay was enrolled in the UK External Quality Assurance Scheme and reports were satisfactory throughout this period.

At diagnosis, all participants with CH had TSH > 375 mU/l and fT4 < 3.9 pmol/l indicating the most severe form of CH. Mean time to treatment with levothyroxine was 14.81 ± 4.39 days (range 10–27 days). Thyroid hormone concentrations at 1–2 months of age were retrieved from records. Mean fT4 concentration was 20.2 pmol/l with a range of 9.4–30.5 pmol/l and reference range of 19–39 pmol/l. Sixty-five percent of participants had an fT4 concentration in the normal range by 1–2 months of age. Mean TSH concentration was 48.5 mU/l with a range of 4.3–172.0 mU/l and reference range of < 6 mU/l. Only one participant had a TSH concentration under 6 mU/l and normalized fT4 concentrations by 1–2 months of age, although all participants had significant biochemical improvement within this timeframe. On the basis of radioisotope scans conducted at diagnosis, sixteen children had confirmed agenesis of the thyroid gland and two had normally positioned thyroid glands suggestive of complete dyshormonogenesis.

No information was gathered about control participants' thyroid status either at time of testing or at screening. All parents of controls were asked about immediate family history of thyroid disorders and about issues with pregnancy and birth, including gestational age and any treatment for jaundice. One control participant was the brother of a participant with CH. All controls were born at full term and one received phototherapy for jaundice.

2.2. MRI acquisition

As part of a larger study, all children underwent structural and resting state functional MR imaging with a total imaging time of about 30 min. Parents were sent a link to a video of the scanning procedure prior to participation so that children knew what to expect. Participants were able to watch a DVD of their choice during the structural elements of scanning (e.g. a children's TV show or film).

MR imaging was carried out on a 3 Tesla Magnetom Prisma system (Siemens, Erlangen, Germany). A T1-weighted three-dimensional MP-RAGE (magnetization-prepared rapid gradient-echo) scan was acquired with a flip angle of 8°. Repetition time was 2300 ms and echo time was 2.74 ms. Voxel size was 1 mm isotropic and 240 slices were obtained. Scan time was 5 m 21 s. One experienced neuroradiologist (KM) blinded to group status reviewed all T1-weighted images for gross anatomical abnormalities.

Multi-shell diffusion MRI (msdMRI) consisting of a multi-band spin-echo diffusion-weighted echo planar imaging (EPI) sequence with 120 unique gradient directions (60 b = 1000 s/mm^2 and 60 b = 2200 s/mm^2), uniformly distributed and interleaved with 14 images without diffusion weighting (b = 0 s/mm^2) of which one has negative phase encode direction for susceptibility distortion correction. Repetition time was 3050 ms with echo time of 60 ms. Multi-band acceleration factor was 2. Voxel size was 2 mm isotropic with a 0.2 mm slice gap and 66 axial slices were obtained. Scan time was 7 m 16 s.

2.2.1. Image analysis

We consider two SMT models for the microscopic diffusion process, a microscopic diffusion tensor (Kaden, Kruggel, et al., 2016) and a multi-compartment model (Kaden et al., 2016a). The first model provides an estimate of microscopic fractional anisotropy (μFA) that measures the degree of directionality of the local diffusion process arising from the microscopic structures in brain tissue. The second microscopic model maps more biologically specific metrics such as neurite density and intrinsic diffusivity that are not influenced by any orientation effects. Standard DTI and SMT based on multi-shell diffusion MRI are used to assess the microstructural properties of white matter in children with CH.

Visual inspection of multi-shell diffusion MRI data was carried out to check for the presence of motion artifacts. Volumes with artifacts present were removed. Data were preprocessed using TractoR version

2.6 (Clayden et al., 2011) and FMRIB Software Library (FSL) version 5.0 (Jenkinson et al., 2012). In brief, brain extraction was performed on a reference b = 0 s/mm^2 volume for each subject (Smith, 2002). The susceptibility-induced off-resonance field was estimated from a pair of b = 0 s/mm^2 images acquired with reversed phase encoding. This off-resonance field was used to correct the susceptibility-induced distortions in all images of the diffusion dataset (Andersson et al., 2003; Smith et al., 2004). Eddy-current induced distortions were corrected for using FSL's eddy tool (Andersson and Sotiropoulos, 2016). At each voxel, a diffusion tensor was estimated using a weighted least-squares regression procedure to calculate standard voxel-wise measurements of FA and MD using both b-shells. Axial diffusivity (AD – representing the diffusion coefficient parallel to the principal diffusion direction) and radial diffusivity (RD – representing the average diffusion coefficient perpendicular to the principal diffusion direction) were also calculated.

After adjustment of the diffusion signal to reduce the Rician-noise induced bias, the microscopic diffusion tensor (Kaden, Kruggel, et al., 2016) and the multi-compartment model (Kaden, Kelm, et al., 2016) were fitted voxel by voxel to the multi-shell diffusion data using the SMT. The microscopic tensor model provides estimates of the microscopic diffusivities parallel and perpendicular to the neurites, from which the microscopic fractional anisotropy is calculated. The SMT multi-compartment model maps the intra-neurite volume fraction and intrinsic diffusivity unconfounded by the effects of fiber crossings and orientation dispersion. Once the microscopic diffusion process was estimated, the fiber orientation distribution was recovered using spherical deconvolution for both models. This did not show any significant differences, and subsequently the orientation dispersion entropy was computed (Kaden, Kelm, et al., 2016). This is a scalar metric which summarizes the directional tissue heterogeneity. The software is available online at https://ekaden.github.io.

Tract-based spatial statistics (Smith et al., 2006) was carried out using FSL version 5.0 and was used to analyze the DTI and SMT parameters. All subject data were then transformed to MNI space. To improve alignment, a study-specific template was generated to which all the subjects were registered. A mean FA skeleton was created by aligning the FA images of all subjects to the most typical subject and thresholding (at FA = 0.2) to suppress areas of high intersubject variability or low mean FA. Each subject's aligned FA image was then projected onto the mean FA skeleton and voxelwise statistics were carried out on the skeleton FA data across subjects. Other diffusion parameters from the DTI and SMT models were projected onto the skeleton in a similar manner and these values used for voxel-wise analysis. Statistical tests were performed using FSL's randomize tool with 5000 random permutations to ensure convergence. Threshold-Free Cluster Enhancement (TFCE) was used as per the tract-based spatial statistics protocol to find clusters in data by comparing neighboring voxels to identify similarities, thereby increasing confidence that the results in each voxel had not occurred by chance. Family-wise error (FWE) correction was used to reduce the likelihood of type I error.

Imaging data were excluded for participants where the imaging protocol was not completed or where there were excessive motion artifacts in the images. One control participant declined to be scanned. Scans were visually inspected and three participants (one female, age = 8.27 ± 3.28), all from the clinical group, were excluded because of poor quality DTI data due to head motion. Chi-square testing showed no significant difference between children with CH and controls for the number of participants excluded due to motion ($\chi^2 = 1.52$, $p = .22$). The final data set used for image analysis included 14 children with CH and 19 controls.

2.3. Behavioral test battery

2.3.1. Nonverbal IQ

The Matrix Reasoning and Block Design subtests of the Wechsler Abbreviated Scale of Intelligence (WASI-II; Wechsler, 1999) were used to estimate performance IQ (standard score mean = 100, SD = 15; individual test standard score mean = 50, SD = 10).

2.3.2. Auditory assessment

Pure-tone audiometry (PTA) was carried out at 0.25, 0.5, 1, 2, 4, and 8 kHz with air conduction, and bone conduction where necessary, to evaluate hearing sensitivity (British Society of Audiology, 2011) with results being reported for speech-frequency PTA (mean of thresholds at 0.5, 1, 2 and 4 kHz). Otoscopy and tympanometry were also conducted to check for outer and middle ear problems.

Speech-in-noise abilities were measured using the Children's Coordinate Response Measure (CCRM; Messaoud-Galusi et al., 2011), an adaptive, non-standardized test based on an adult version (Bolia et al., 2000; Brungart, 2001). During this test, participants heard a series of low-context sentences using the carrier phrase “show the dog where the *[colour] [number]* is” with colours being black, white, green, red, blue or pink, and numbers being between one and nine, excluding bisyllabic seven. Energetic masking was added in the form of a speech-shaped noise masker. Participants were required to indicate what they heard via a response panel on a computer screen. Sentences were presented via Sennheiser HD25SPII headphones, with both speech and noise presented diotically. The output level of the test was kept constant at 70 dB SPL and a three-up, one-down adaptive procedure was used to vary the signal-to-noise ratio (SNR) and track 79.4% correct on the psychometric function (Levitt, 1971). The first sentence was presented at a SNR of +20 dB. A correct response resulted in a decrease in the level of the speech and increase in the level of the noise, with an initial step size of 10 dB and subsequent linear decrease over the first two reversals to a 5 dB step size. Testing terminated after the first of either six reversals or 30 trials and the mean of the last four reversals was calculated as the threshold. The task was carried out twice in succession and the mean of the two scores used in the analyses. A higher score indicates poorer ability to hear speech in the presence of background noise.

2.3.3. Language and communication

Core language ability was assessed using the Clinical Evaluation of Language Fundamentals – Fourth Edition UK (CELF-4; Semel et al., 2003). Four subtests were administered for each participant, dependent on age, in order to derive the core language score, which includes elements of receptive and expressive language and language memory. The age dependency was as follows: all participants performed ‘recalling sentences’ and ‘formulated sentences’. Participants aged 6–12 years additionally performed ‘concepts and following directions’ and ‘word structure’; those aged 9–12 years additionally performed ‘concepts and following directions’ and ‘word classes-2’ (which includes ‘word classes expressive’ and ‘word classes receptive’); and those age 13–16 years performed ‘word classes-2’ and ‘word definitions’. The core language score is a standardized score with a mean of 100 and standard deviation (SD) of 15. Each subtest has a mean of ten and a SD of three with norms available from ages 5 to 16 years.

Communication skills were assessed using the Children's Communication Checklist (CCC-2; Bishop, 2003). The CCC-2 is a well-validated, standardized parental questionnaire designed to screen for communication problems in children aged 4–16 years. It comprises 70 items which are divided into 10 scales: Speech, Syntax, Semantics, Coherence, Inappropriate Initiation, Stereotyped Language, Use of Context, Nonverbal Communication, Social Relations, and Interests. Parents respond to each item on a four point scale rating frequency with which behaviors are observed from 0 (never or less than once a week) to 3 (several times a day or always). Two or more scales below the fifth percentile indicate a clinically significant communication problem. Two composite scores were obtained: the General Communication Composite (GCC), which is derived from the first eight scales and identifies those children at risk of communication difficulties, and the Social Interaction Deviance Composite (SIDC), which identifies children who

have social communication difficulties that are disproportionate to their structural language difficulties. Validation studies have shown that the CCC-2 is a useful screening tool which is able to identify over 90% of children with communication difficulties from the typically developing population (Norbury et al., 2004). Scores of ≥55 on the GCC and ≥ 0 on the SIDC are indicative of typical development; Scores of < 55 on the GCC and ≥ 0 on the SIDC identify children who fall within the bottom 10% of the population on communication measures; Scores of < 55 on the GCC and < 0 on the SIDC suggest the presence of Higher-Order Social Interaction Disorder (HOSID), characteristic of children with a pragmatic language disorder, or autism spectrum disorder (ASD); And scores of < −15 on the SIDC (regardless of GCC) are indicative of clinically significant ASD (Norbury et al., 2004).

2.4. Statistical analysis

Group comparisons were made using unpaired Student's *t*-tests for normally distributed data or Mann-Whitney *U* tests for non-normal data. Hearing, language, and communication skills assessment scores were compared using analysis of covariance (ANCOVA) controlling for performance IQ.

Age and sex are known to affect brain growth and myelination. In general, increases in FA and decreases in MD are observed with increasing age with widespread changes noted across the brain (Barnea-Goraly et al., 2005; Qiu et al., 2008; Schmithorst et al., 2002). Sexual dimorphism has been noted using DTI with widespread structural differences observed between males and females between the ages of 8 and 16 years, characterized by higher FA and lower MD in females compared with males (Clayden et al., 2012; Seunarine et al., 2016); Therefore, age and sex were included as covariates in the tract-based spatial statistics analysis. IQ has also been shown to be associated with diffusion metrics with significant positive correlations demonstrated between FA and IQ and negative correlations between MD and IQ (Schmithorst et al., 2005); Therefore, performance IQ was also added as a covariate in the analyses.

3. Results

3.1. Qualitative neuroradiological review

All scans were evaluated for gross abnormalities by an experienced pediatric neuroradiologist (KM). Incidental findings were reported for one participant with CH (empty sella) and one control (bulbous internal auditory meatus). These were not thought to be of clinical significance and the participants' images remained in the analysis. All other scans were reported as normal. The groups did not differ significantly on number of incidental findings ($\chi^2 = 0.01$, $p = .906$).

3.2. Diffusion-based microstructure imaging

The results of tract-based spatial statistics analysis comparing children with CH and controls are shown in Fig. 1. After controlling for the effects of age, gender and performance IQ, FA was significantly lower in children with CH ($p < .05$, FWE corrected) in the cerebellum, bilateral thalami and the right temporal lobe. Significant increases in RD were also seen for the children with CH ($p < .05$, FWE corrected), again in the cerebellum and bilateral thalami. There were no differences seen in MD or AD (data not shown). The SMT model parameters showed significantly lower microscopic FA and intra-neurite volume fraction, and higher transverse microscopic diffusivity in the children with CH compared with controls, again in areas including the cerebellum and thalamus, and also in the occipital lobe, corpus callosum and in the white matter adjacent to the sensorimotor cortex, particularly in the left hemisphere.

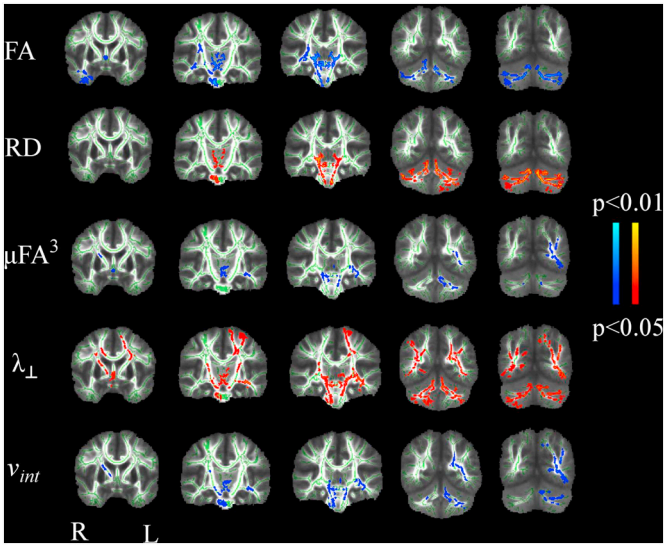

Fig. 1. Coronal slices of the cohort's mean white matter skeleton (shown in green) overlaid with tract-based spatial statistics results. Blue clusters represent voxels with significantly lower values in the children with congenital hypothyroidism compared with controls. Red-yellow clusters represent voxels with significantly higher values in the children with congenital hypothyroidism compared with controls. Diffusion parameters (with number of significant voxels in brackets) are: FA = fractional anisotropy (10877), RD = radial diffusivity (13324), μFA^3 = microscopic FA cubed (5178), $\lambda_\perp$ = transverse microscopic diffusivity (29856), v_{int} = intra-neurite volume fraction (9949). All results $p < .05$, FWE corrected.

3.3. Behavioral assessments

3.3.1. Group analyses

Table 1 shows the characteristics of the CH and control groups who completed the behavioral test battery, together with between-group statistical comparisons. The groups did not differ on age, sex or socioeconomic status. However, as a group, children with CH obtained significantly poorer Performance IQ and Block Design scores relative to controls ($p = .029$ and $p < .001$ respectively; see Table 1). In addition, they had significantly poorer mean speech-frequency PTA thresholds ($p = .005$), although the majority of children with CH (76%) had PTA thresholds that were within normal limits (≤20 dB HL) at all frequencies tested. Removing the four children who had elevated PTA thresholds from the analysis still resulted in a significant difference in mean speech-frequency PTA thresholds between groups, driven by the higher (poorer) thresholds of the CH group ($M = 6.54$ dB HL, $SD = 3.99$) relative to controls ($M = 3.41$ dB HL, $SD = 4.16$; $p = .040$). Children with CH obtained mean speech-in-noise scores that were significantly poorer than those of controls ($p = .012$), scoring on average more than one SD above (i.e. worse than) the control group. There was a marginally significant difference between groups for CELF core language ($p = .050$), with the CH group performing on average 14 points (i.e. ~ 1 SD) below controls on this measure (see also Supplementary Table 1). Finally, children with CH obtained lower GCC (but not SIDC) scores relative to controls ($p = .015$ and $p = .058$, respectively).

3.3.2. Individual differences

Group means masked considerable individual differences, and therefore the performance of individual children with CH was explored. The demographic and medical characteristics and results of the CH participants on the behavioral test battery are shown in Table 2. Regarding nonverbal IQ, while the majority of children in the CH group obtained Performance IQ scores within the normal range or better (i.e. > 85), two (12%) did not (Performance IQ scores of 76 and 84; see also Supplementary Fig. 2). For Block Design, five participants in the

Table 1
Participant characteristics and between group comparisons.

	Congenital hypothyroidism (n = 17)			Controls (n = 20)						
Variable	*M*	*SD*	Range	*M*	*SD*	Range	Statistic (df)	*p*	Effect size	95% CI
Age (years)	9.66	2.26	6.24–15.44	10.49	2.97	7.26–16.06	$W(35) = 149$	0.537	−0.11	[−0.24, 0.99]
Sex	11F:6M	_	_	11F:9M	_	_	$\chi^2(1) = 0.36$	0.549	1.68	[−6.36, 25.77]
Socio-economic status	16.80	10.78	4.42–42.80	12.04	9.35	3.302–43.08	$W(35) = 208$	0.141	0.28	[−0.55, 8.79]
Performance IQ	99.35	13.91	76–126	109.25	12.08	90–129	$t(32) = -2.29$	**0.029**	−0.75	[−18.7, −1.09]
Block design	44.82	9.78	25–61	56.20	8.50	38–69	$t(32) = -3.74$	**< 0.001**	−1.23	[−17.57, −5.18]
Matrix reasoning	54.00	11.22	33–74	54.95	7.63	40–72	$t(27) = 0.77$	0.770	−0.10	[−7.54, 5.64]
Auditory performance										
Speech-frequency PTA (dB HL)	8.27	5.48	1.25–21.88	3.41	4.16	−1.88 - 12.50	$W(35) = 263.00$	**0.005**	0.47	[1.25, 7.50]
Speech-in-noise (SNR)	−4.38	2.61	−7.75–0.85	−6.46	0.94	−7.90–4.75	$F(1) = 7.09$	**0.012**	1.09	[−3.13, −0.42]
CELF core language	97.65	19.81	58–127	112.35	8.76	96–129	$F(1) = 4.12$	0.050	−1.08	[0.00, 15.98]
CCC-2										
GCC	60.76	26.67	18–106	83.80	14.71	51–101	$F(1) = 6.60$	**0.015**	−1.11	[3.92, 33.53]
SIDC	3.24	8.73	−11–22	−3.45	9.02	−20–18	$F(1) = 3.86$	0.058	0.73	[−12.74, 0.22]

Comparisons on scale data were *t*-tests (performance IQ and subtests), Mann-Whitney U tests (age, socio-economic status and speech-frequency PTA) or ANCOVA controlling for performance IQ (speech-in-noise, CELF core language, CCC-2 GCC and SIDC). Group comparisons on sex were done using Chi-squared tests (one-sided). Significant comparisons ($p < .05$) are shown in boldface. Effect size = Cohen's *d* for *t*-test, Mann-Whitney *U* tests and ANCOVA, and odds ratio (OR) for Chi-squared tests. CI = confidence interval.
CELF = Clinical Evaluation of Language Fundamentals – Fourth Edition UK, CCC-2 = Children's Communication Checklist 2, GCC = General Communication Composite, SIDC = Social Interaction Deviance Composite.
Significant differences between groups are shown in bold

CH group (29%) scored more than one SD below the mean (compared with one participant in the control group). Four children in the CH group (24%) had PTA thresholds that were outside normal limits. One of these had a unilateral left-sided mild-to-moderate sensorineural hearing loss (speech-frequency PTA of 40 dB HL), and three had mild hearing losses (thresholds between 20 and 40 dB HL) in the high frequencies (4–8 kHz), one unilaterally on the right, the other two bilaterally (see Supplementary Fig. 3). Four (24%) of the CH group obtained core language scores that were indicative of clinically significant language difficulties (i.e. ≥ 1 SD below the population mean). Poor performance on individual subtests was also common in the CH group with eight participants (47%) scoring ≥1 SD below the population mean on at least one subtest (see Supplementary Fig. 4). Finally, seven children in the CH group (41%) obtained a GCC score of < 55 (compared to one child in the control group). However, all children in the CH group obtained a SIDC score > 15 (see Supplementary Fig. 5), indicating difficulties in structural language rather than social/pragmatic difficulties.

3.4. Correlations between diffusion measures and clinical scores

Correlations between diffusion measures and TSH concentrations at 1–2 months, hearing, language, and communication were examined for the CH group, controlling for age, sex, and performance IQ (see Table 3). Significant correlations were detected between DTI and SMT parameters and speech-in-noise scores when controlling for age, sex, and performance IQ. For speech-in-noise, more negative scores indicate better performance; therefore, a negative correlation with FA demonstrates a positive correlation with speech-in-noise performance. Fig. 2 shows examples of correlations (where > 5000 voxels were detected) between diffusion metrics and speech-in-noise scores. Areas of association included the right parietal lobe (FA), the genu, isthmus and splenium of the corpus callosum, cerebellum and left occipital lobe, and the parietal lobes bilaterally (MD and RD). Of the diffusion metrics tested, RD produced the largest number of significant voxels with comparable correlation coefficients across the DTI and SMT parameters tested (with the exception of the multi-compartment intrinsic diffusivity). Fig. 3 shows individual plots of selected diffusion metrics versus speech-in-noise scores (where > 5000 voxels were detected).

Significant correlations were also detected between DTI and SMT parameters and CELF core language scores when controlling for age, sex, and performance IQ. In this case the longitudinal microscopic diffusivity from the microscopic tensor model detected the largest number of voxels demonstrating correlation with CELF core language scores. Fig. 4 shows examples of correlations between diffusion metrics and CELF core language scores (where > 5000 voxels were detected). Plots of selected diffusion metrics (where > 5000 voxels were detected) versus CELF core language scores are shown in Fig. 5.

Significant correlations were detected between DTI and SMT parameters and CCC-2 GCC scores when controlling for age, sex, and performance IQ. Similarly to CELF core language, the longitudinal microscopic diffusivity from the microscopic tensor model detected the largest number of voxels demonstrating correlation with CCC-2 GCC scores. Examples of correlations between diffusion metrics and CCC-2 GCC scores (where > 5000 voxels were detected) are shown in Fig. 6. Plots of selected diffusion metrics (where > 5000 voxels were detected) versus CCC-2 GCC scores are shown in Fig. 7.

Finally, no significant correlations were observed between any of the diffusion metrics and TSH concentrations at 1–2 months, or between diffusion metrics and speech-frequency PTA.

4. Discussion

The aim of this study was to evaluate the effect of early treated severe CH on the development of white matter integrity, hearing, cognition, language and communication in children. We identified reductions in white matter microstructural integrity in children with a history of severe CH. Decreases in FA and increases in RD suggest a reduction in the density and/or increase in orientation dispersion of white matter microstructure in children with CH compared with typically developing controls, particularly in areas including the cerebellum, thalamus and right temporal lobe. Moreover, the severe CH group on average had poorer hearing, nonverbal IQ, core language, and communication skills than typically developing controls. Abnormalities in white matter fiber density were associated with listening, language and communication difficulties in children with CH.

Table 2
Demographic and medical characteristics of CH participants together with individual performance on standardized tests.

Participant	Age (years)	Sex	Time to treatment (days)	T4 at 1-2 months (pmol/l)	TSH at 1-2 months (mU/l)	Performance IQ	Pure tone hearing	Core language	CCC2-GCC	CCC2-SIDC
1	11	M	19	9.4	55.5	87	WNL	79	39	6
2	10	F	12	24.7	32.5	84	Unilateral MMHL	94	83	-7
3	6	F	15	19.2	71.2	119	WNL	127	86	-6
4	9	F	16	16.0	23.5	98	WNL	100	78	22
5	8	F	13	22.4	38.5	126	Unilateral HFHL	114	50	12
6	10	M	17	15.6	172.0	76	WNL	96	59	-2
7	12	F	15	25.0	4.3	96	WNL	127	92	-1
8	9	F	12	21.8	12.5	98	WNL	111	106	1
9	9	M	10	30.5	11.3	109	WNL	115	90	-1
10	9	M	10	25.4	39.9	116	WNL	109	18	9
11	12	M	14	15.6	34.4	89	Bilateral HFHL	70	34	6
12	11	F	20	23.0	66.1	86	WNL	72	22	7
13	8	F	Unknown	19.0	158.0	85	WNL	87	36	17
14	8	F	11	22.7	12.4	99	WNL	58	42	2
15	7	M	12	11.9	83.5	106	WNL	109	82	6
16	8	F	14	16.5	88.5	105	WNL	90	57	-5
17	15	F	27	24.2	29.6	110	Bilateral HFHL	102	59	-11

Shaded values represent performance below the standardized normal range or outside of recommended treatment guidelines.
T4 reference range = 19–39 pmol/l.
TSH concentration reference range < 6 mU/l.
Performance IQ standard score mean = 100, SD = 15.
PTA normal limits ≤20 dB HL at any frequency from 0.25 to 8 kHz. WNL = within normal limits, MMHL = mild-moderate hearing loss, HFHL = high-frequency hearing loss.
Core language score mean = 100, SD = 15.
GCC ≥ 55 and SIDC ≥0 is indicative of typical development; GCC < 55 and SIDC < 0 suggests the presence of Higher-Order Social Interaction Disorder (HOSID), characteristic of children with a pragmatic language disorder, or autism spectrum disorder (ASD); SIDC < −15 (regardless of GCC) is indicative of clinically significant ASD.

4.1. Brain development

Analysis of SMT derived parameters was carried out in order to distinguish between microstructural density and orientation effects. This indicated decreases in microscopic FA and intra-neurite volume fraction, and increases in transverse microscopic diffusivity. There are two potential reasons for an increase in transverse microscopic diffusivity: a lower axon density (as suggested by the decrease in intra-neurite volume fraction) and/or a lower degree of myelination. Differences in transverse microscopic diffusivity reveal more widespread anatomical differences than is obtained with conventional DTI parameters suggesting that SMT parameters may provide more sensitive biomarkers of white matter change in CH.

Thyroid hormones are essential for growth and development, particularly for brain development. There are strong relationships between the timing of thyroid hormone action and various developmental processes, with thyroid hormone influencing very specific neurophysiological functions (Rovet, 2014; Zoeller and Rovet, 2004). The protective action of maternal thyroid hormone in utero enables neurogenesis and neuronal migration to continue unaffected until about the first trimester. In typical development, the fetal thyroid gland secretion begins in the second trimester with the developing brain then deriving thyroid hormones from both the mother and the fetus. However, if CH is present, and with the abrupt cut-off of the maternal supply at birth, processes including myelination, glial cell proliferation, synapse formation, and axon and dendrite migration and branching are disrupted. White matter development, and particularly the process of myelination, is imperative for establishing and sustaining effective brain communication and therefore any disturbance in this process may lead to diminished brain connectivity or disruption of brain messaging (Deoni et al., 2012).

Rodent models of hypothyroidism have demonstrated delays in cell

Table 3
Correlations between clinical scores and diffusion metrics in children with congenital hypothyroidism.

		Clinical score														
		TSH concentration at 1–2 months			PTA			Speech-in-noise			CELF core language			CCC2 (GCC)		
Model	**Parameter**	**No. sig voxels**	***r***	***p***	**No. sig voxels**	***r***	***p***	**No. sig voxels**	***r***	***p***	**No. sig voxels**	***r***	***p***	**No. sig voxels**	***r***	***p***
Standard DTI model	FA	0	_	_	0	_	_	8997	−0.90[a]	**< 0.001**	0	_	_	7	0.81[a]	**< 0.001**
	MD	0	_	_	0	_	_	48,825	0.77[a]	**0.001**	36,523	−0.47	0.103	37,221	−0.80[a]	**< 0.001**
	RD	0	_	_	0	_	_	62,015	0.87[a]	**< 0.001**	30,909	−0.67	0.013	20,096	−0.85[a]	**< 0.001**
	AD	0	_	_	0	_	_	0	_	_	0	_	_	17,751	−0.82[a]	**< 0.001**
Microscopic tensor model	$\lambda_{\|\|}$	0	_	_	0	_	_	1500	0.75[b]	**0.002**	48,664	−0.70	0.008	47,747	−0.89[a]	**< 0.001**
	$\lambda_{\perp}$	0	_	_	0	_	_	50,628	0.80[b]	**< 0.001**	860	−0.67	0.012	1439	−0.80[b]	**< 0.001**
	μFA^3	0	_	_	0	_	_	0	_	_	0	_	_	0	_	_
	FOD (micro)	0	_	_	0	_	_	21,199	−0.86[a]	**< 0.001**	5596	0.68	0.010	98	0.84[a]	**< 0.001**
Multi-compartment model	v_{int}	0	_	_	0	_	_	38,841	−0.84[a]	**< 0.001**	0	_	_	0	_	_
	λ	0	_	_	0	_	_	402	0.44[b]	0.117	0	_	_	3892	−0.72[b]	**0.004**
	λ^{ext}	0	_	_	0	_	_	2339	0.77[b]	**0.001**	40,908	−0.74	**0.004**	32,761	−0.87[a]	**< 0.001**
	FOD (multi)	0	_	_	0	_	_	3771	−0.95[a]	**< 0.001**	0	_	_	0	_	_

r = correlation coefficient.
FA = fractional anisotropy, MD = mean diffusivity, RD = radial diffusivity, AD = axial diffusivity, $\lambda_{||}$ = longitudinal microscopic diffusivity, $\lambda_{\perp}$ = transverse microscopic diffusivity, μFA^3 = microscopic fractional anisotropy (cubed), FOD (micro) = fiber orientation dispersion (microscopic tensor model), v_{int} = intra-neurite volume fraction, λ = intrinsic diffusivity, λ^{ext} = extra-neurite microscopic mean diffusivity, FOD (multi) = fiber orientation dispersion (multi-compartment model). Correlations remaining significant following Bonferroni correction are shown in bold ($\alpha = 0.005$).
[a] Pearson correlation.
[b] Spearman correlation.

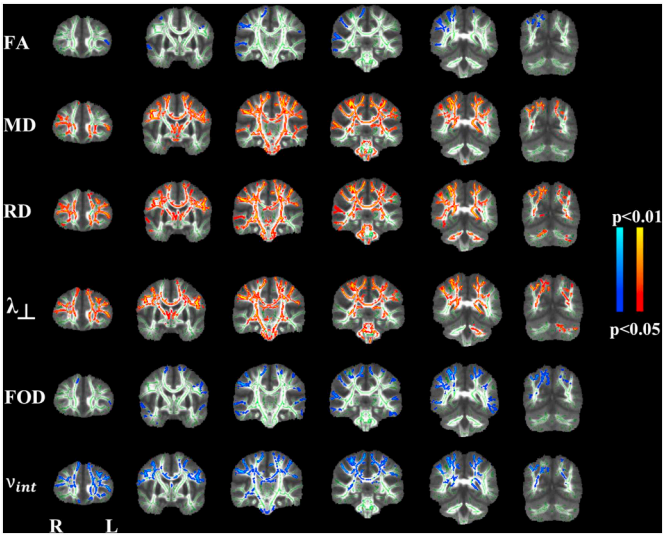

Fig. 2. Examples of associations between speech-in-noise scores and DTI and SMT diffusion metrics. Blue clusters represent voxels with significant negative correlation between diffusion metrics and speech-in-noise scores. Red-yellow clusters represent voxels with significant positive correlation between diffusion metrics and speech-in-noise scores. FA = fractional anisotropy, MD = mean diffusivity, RD = radial diffusivity, $\lambda_{\perp}$ = transverse microscopic diffusivity, FOD = fiber orientation dispersion (from SMT microscopic tensor model), v_{int} = intra-neurite volume fraction. All results $p < .05$, FWE corrected. Associations were also seen for longitudinal microscopic diffusivity, intrinsic diffusivity, extra-neurite microscopic mean diffusivity and FOD (from the multi-compartment model) but, for brevity, only those with correlations in > 5000 voxels are shown.

migration and branching, synapse formation and myelination (Balazs et al., 1969; Barradas et al., 2001; Bernal, 2002), as well as deficiencies in cerebellum development, particularly affecting the Purkinje cells (Bernal, 2002). The white matter alterations observed in the current study suggest that CH in humans also disrupts white matter development, particularly in the cerebellum, in common with observations in rats.

4.2. Hearing, cognition, language, and communication

Despite their early lack of thyroid hormone, the majority of children with a history of severe CH performed within the standardized population range in domains of hearing, nonverbal IQ, language, and communication. However, four points are worth highlighting in this respect. First, the standardisation samples used for the nonverbal and language assessments were collected in 2010/11 and 2000 respectively. The "Flynn effect" refers to the observed rise in IQ scores over time (Flynn, 1984). Therefore, it is possible that current norms would be higher due to upward secular drift, meaning that more of the CH group would be below contemporary standards had more recently standardized tests been used. This possibility is supported by the second point, that as a group, the children with CH in this study performed significantly more poorly than their typically developing peers on measures of speech-frequency PTA, speech-in-noise perception, nonverbal IQ, core language, and communication. Third, the CH group contained a number of children who showed clinically significant deficits on each of the hearing, cognition, language and communication measures. Fourth, a relatively high percentage (41%) of the CH group obtained parental report scores that were indicative of clinically significant difficulties with language and communication. Consequently, despite the average good performance of children with a history of severe CH in this study, our findings nonetheless suggest that these children may be at increased risk of deficits in hearing, language, and communication compared to typically developing controls (Alvarez et al., 2004; Bargagna et al., 2000; S. I. Song et al., 2001).

Reduced performance on the composite IQ score in the hypothyroid group appeared to be driven by poorer ability to complete Block Design testing compared to Matrix Reasoning, with Matrix Reasoning showing no significant difference between groups. Performance on Matrix Reasoning is known to be affected by verbal abilities (Baldo et al., 2015) and language abilities were within the population normal range for the majority of the congenital hypothyroid group. Block Design assesses spatial visualisation, visual-motor control and abstract conceptualisation. Previous studies have suggested that children with CH have difficulties with visuospatial processing (Rovet, 1999a; Rovet et al., 1992; Simic and Rovet, 2016) but this was not measured in this study.

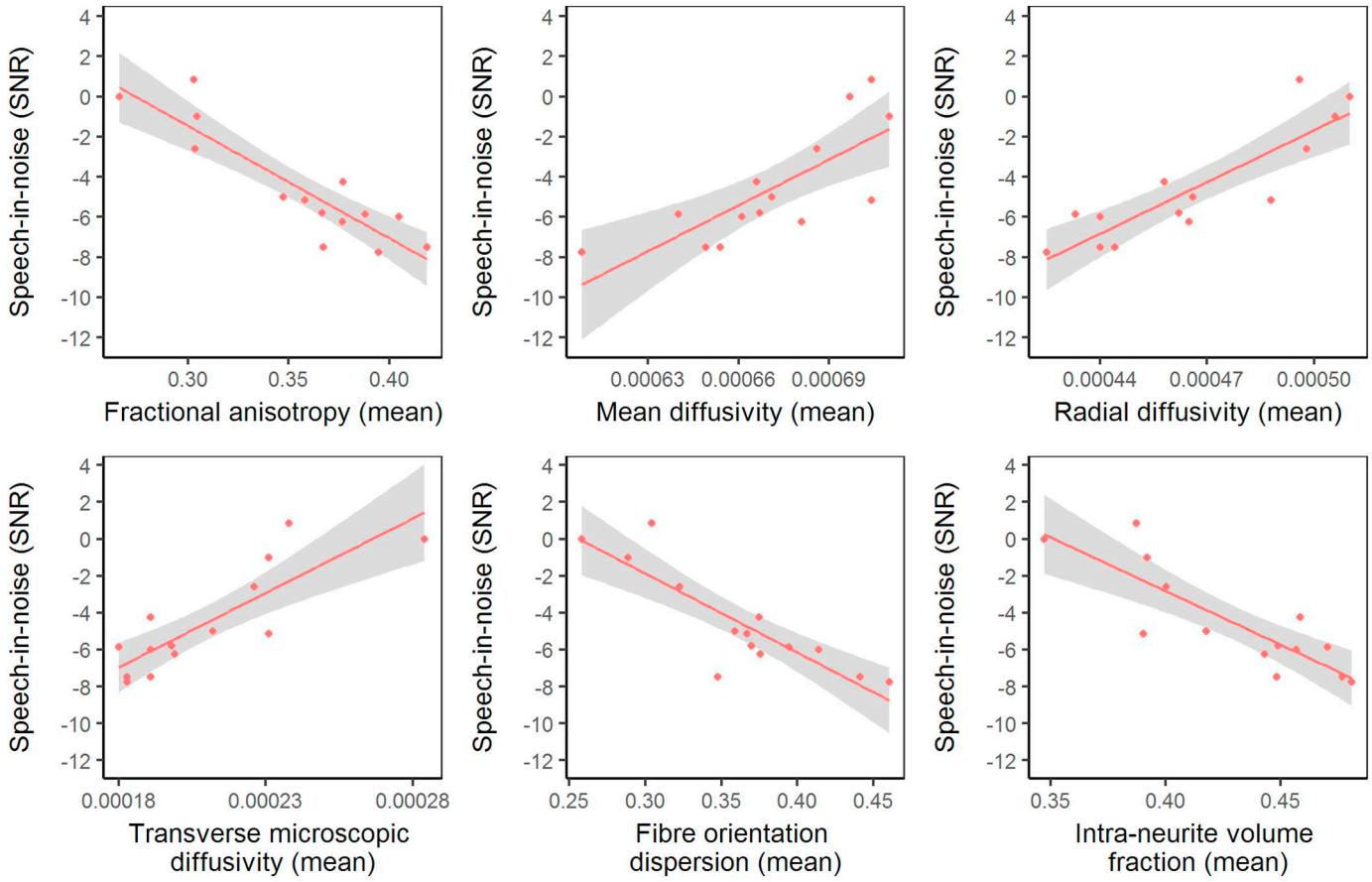

Fig. 3. Plots showing mean values of diffusion data from areas of significant correlation shown in Fig. 2 (FA, MD and RD, $\lambda_{\perp}$, FOD, v_{int}) against speech-in-noise scores.

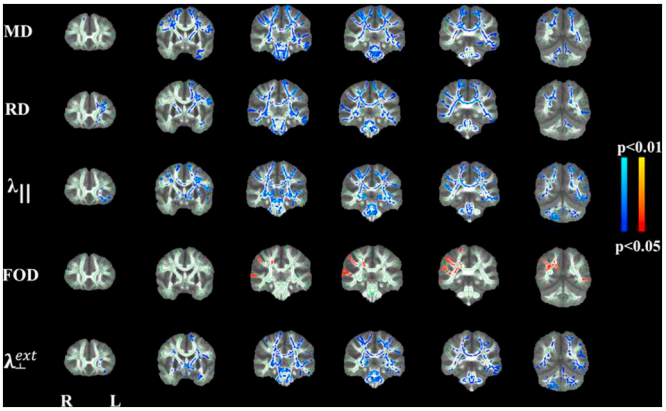

Fig. 4. Examples of associations between CELF core language scores and DTI and SMT diffusion metrics. Blue clusters represent voxels with significant negative correlation between diffusion metrics and core language scores. Red-yellow clusters represent voxels with significant positive correlation between diffusion metrics and speech-in-noise scores. MD = mean diffusivity, RD = radial diffusivity, $\lambda_{||}$ = longitudinal microscopic diffusivity, FOD = fiber orientation dispersion (from SMT microscopic tensor model), λ^{ext} = extra-neurite microscopic mean diffusivity.

Our findings of poorer performance amongst children with a history of severe, early treated CH on measures of speech-frequency PTA and speech-in-noise perception are consistent with the literature. Hearing sensitivity has been shown to be reduced in children and young adults with CH, with those with severe disease being more adversely affected (Bruno et al., 2015; Lichtenberger-Geslin et al., 2013; Rovet et al., 1996). In the current study, 24% of children with CH had clinically significant hearing losses. The combined prevalence of mild bilateral and high-frequency sensorineural hearing loss in the UK is estimated at 0.5% by 11 years of age (Hall et al., 2011). Our findings therefore suggest that severe CH puts children at a significantly greater risk of hearing loss relative to the typically developing population. Speech-in-noise testing also showed that the children with CH had greater problems hearing speech in the presence of background noise than their typically developing peers. This may be due to the increased risk of hearing loss in this group, as children with even mild-to-moderate levels of hearing loss have been shown to require more favourable SNRs in order to adequately hear in the classroom (Crandell and Smaldino, 2000).

Our findings of poorer core language in children with CH are also consistent with the literature (Alvarez et al., 2004; Bargagna et al., 2000). In the general population, around 10% of children have clinically significant language difficulties (Norbury et al., 2016). The prevalence of core language difficulties in the CH group was 24%; i.e., more than double what we would expect in the general population. Several previous studies have shown significant deficits in language development for children with CH, particularly in those aged 5 years and under (Gejao et al., 2009; Gejao and Lamonica, 2008). Several studies have suggested that deficits in language might diminish with age in this group (Bargagna et al., 2000; Rovet et al., 1992). However, the participants in the current study were older than those previously assessed, and there was no correlation between age and core language in the CH group in this study. Our results therefore suggest that severe CH may put children at risk of clinically significant language deficits that persist into adolescence, despite early treatment.

Our findings suggest that children with a history of severe CH are at increased risk of communication difficulties in childhood and adolescence despite early treatment. As a group, children with CH were

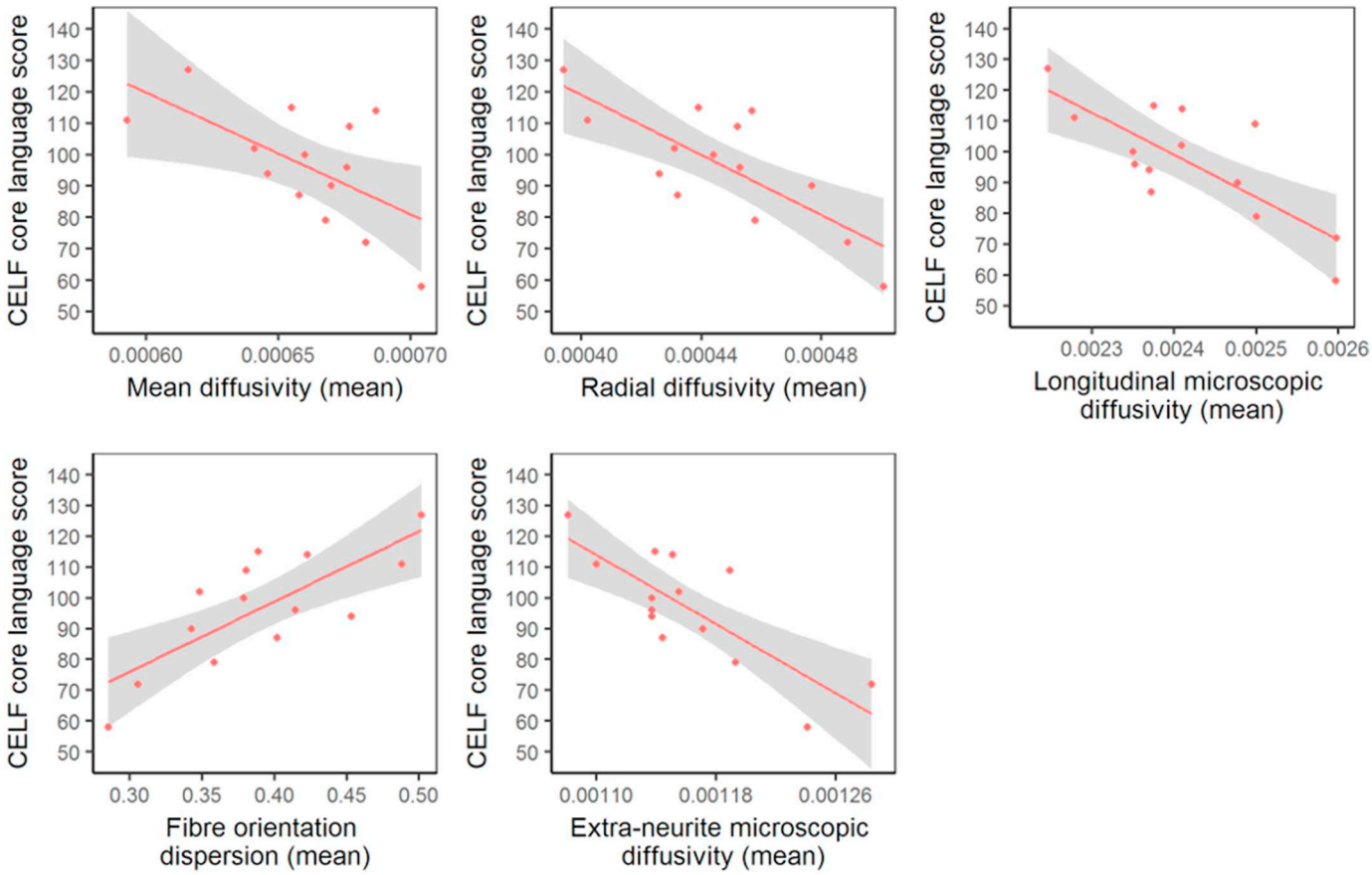

Fig. 5. Plots showing mean values of diffusion data from areas of significant correlation shown in Fig. 4 (MD, RD, $\lambda_{||}$, FOD, λ^{ext}) against CELF core language scores.

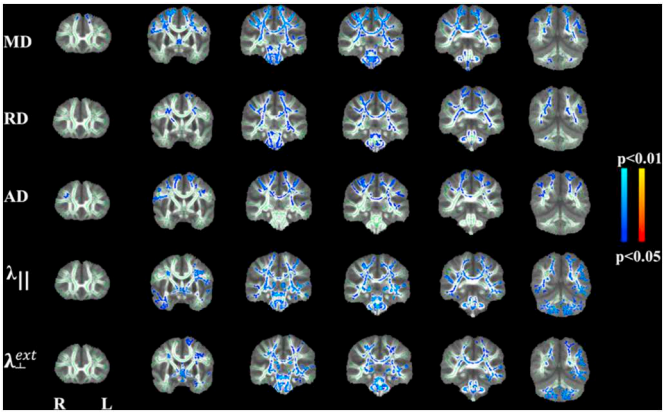

Fig. 6. Examples of associations between parental report communication scores (CCC-2 GCC) and DTI and SMT diffusion metrics. Blue clusters represent voxels with significant negative correlation between diffusion metrics and parental report communication scores. Red-yellow clusters represent voxels with significant positive correlation between diffusion metrics and speech-in-noise scores. MD = mean diffusivity, RD = radial diffusivity, AD = axial diffusivity, $\lambda_{||}$ = longitudinal microscopic diffusivity, λ^{ext} = extra-neurite microscopic mean diffusivity.

reported by parents as having poorer structural language abilities compared with controls. Moreover, a higher proportion of those with CH (41%) obtained parental reports that were indicative of language or communication impairments than would be expected for the general population (i.e., around 10%; Bishop, 2003). These deficits were specific to structural aspects of language rather than aspects of pragmatic or social communication, and none of the children obtained parental report scores that were indicative of pragmatic or social deficits. Therefore, our results suggest that children with severe CH may be at greater risk for structural language deficits than their typically developing peers, but not for autism spectrum disorders, and that these deficits are likely to continue at least into adolescence.

Finally, exploration of individual differences did not uncover a clear pattern of poor performance on behavioral tests nor indicate particular relationships between disease measures in early life and hearing, cognition, language or communication abilities.

4.3. Relationships between brain structure and behavior

The children with a history of severe CH in this study showed significant correlations between speech-in-noise and FA, MD and RD in the right parietal lobe, and more widespread correlations with MD and RD in numerous areas including the genu, isthmus and splenium of the corpus callosum, cerebellum and left occipital lobe, and the parietal lobes bilaterally. SMT parameters showed widespread positive correlations (indicating a negative association with task performance) for transverse microscopic diffusivity and widespread negative associations with intra-neurite volume fraction. Negative correlations with fiber orientation dispersion were observed in superficial white matter indicating greater dispersion with poorer speech-in-noise scores. The SMT model therefore provides greater insight than afforded by DTI alone, allowing changes in fiber dispersion to be unambiguously determined. A previous study of children with no hearing or auditory processing problems has shown negative correlations between FA and performance on a speech-in-noise task, with significant clusters seen in left and right prefrontal cortices, along with positive correlations between FA and task performance in the centrum semiovale bilaterally, reflecting connections with motor regions (Schmithorst et al., 2011). Activation of

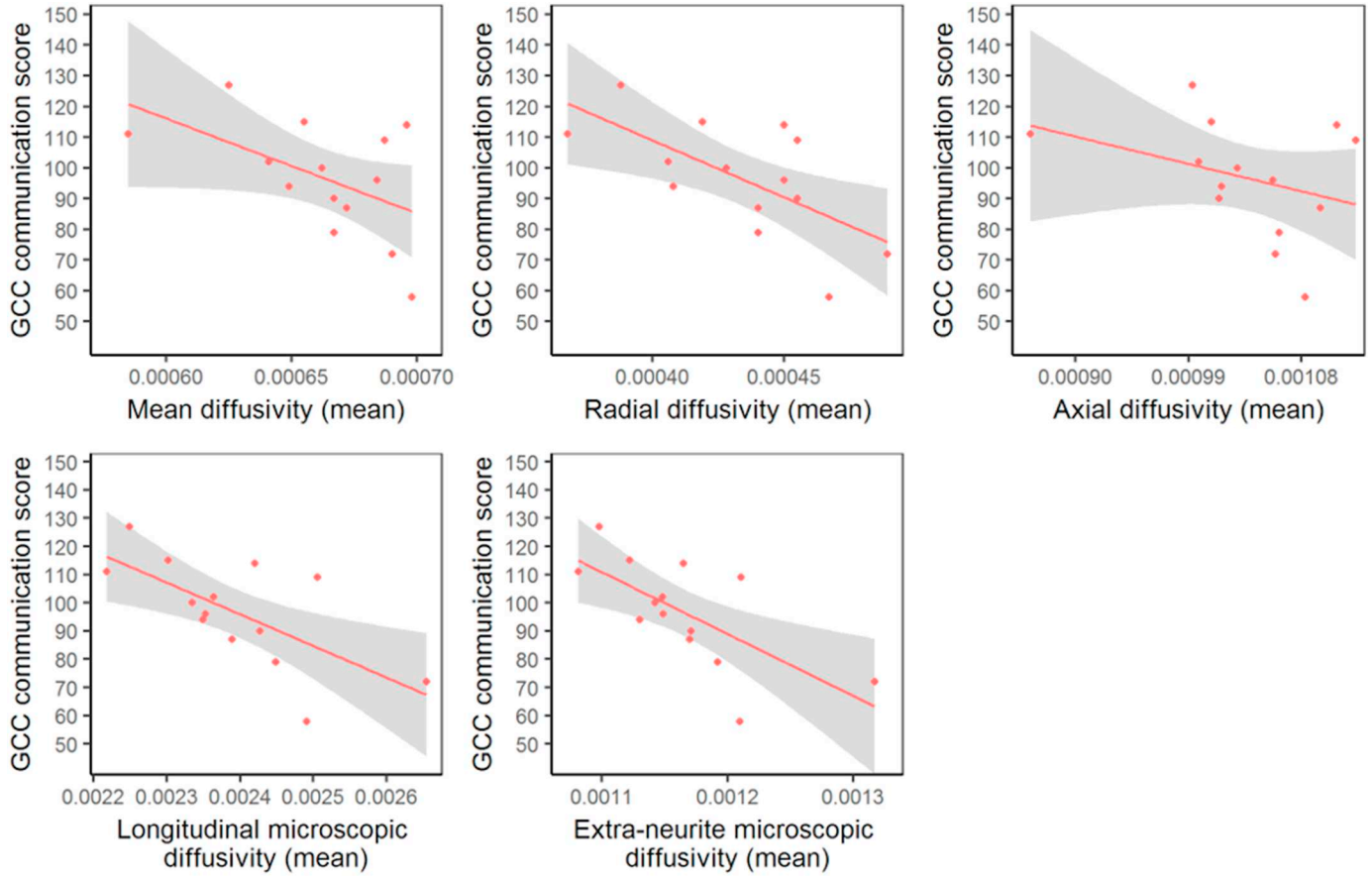

Fig. 7. Plots showing mean values of diffusion data from areas of significant correlation shown in Supplementary Fig. 7 (MD, RD, AD, $\lambda_{||}$, λ^{ext}) against CELF core language score.

the right parietal cortex has previously been associated with processing global auditory changes (Hamada et al., 2004). Furthermore, several studies have found associations between auditory abilities and diffusion metrics, particularly in the corpus callosum (Farah et al., 2014; Owen et al., 2013).

In the CH group widespread negative correlations were seen between core language scores and MD and RD. Longitudinal microscopic diffusivity and extra-neurite microscopic mean diffusivity also showed widespread negative associations with core language. There was also a positive association between fiber orientation dispersion and core language again with poorer performers having more dispersed peripheral white matter structure. Previous studies of the white matter structural correlates of language impairment have suggested a reduction in FA in the superior longitudinal fasciculus (Verhoeven et al., 2012) as well as diffuse changes across the whole brain (Lee et al., 2013; Murner-Lavanchy et al., 2018). Our findings suggest that the language deficits experienced by children with CH may have origins in disordered white matter development and particularly in myelin status as demonstrated by the associations seen between language abilities and RD (S. K. Song et al., 2003).

Strong and widespread negative correlations were also seen between parental report of communication and MD, RD and AD, as well as longitudinal microscopic diffusivity and extra-neurite microscopic mean diffusivity for the children with CH. In addition, the CH group was at significantly greater risk of communication difficulties than controls. Previous studies of adolescents and adults with autism spectrum disorder have examined relationships between white matter microstructure and questionnaire data which included questions about communication ability, and have shown that associations exist between social and communication abilities and diffusion metrics (Bakhtiari et al., 2012). One study noted strong associations between MD and RD and core communication and social features of autism spectrum disorder (Gibbard et al., 2013). However, this is the first study to show significant relationships between parental report communication and white matter microstructure in children with CH suggesting that communication abilities and brain structure are closely related in this group.

4.4. Methodological considerations

Several limitations should be considered when interpreting our results. The first is that we had limited information about TSH and T4 levels in the first months of life and throughout childhood. Many of the participants were seen at GOSH for diagnosis and initial follow-up and were then transferred to their local hospital for long-term follow-up. We only had access to records kept at GOSH. More information about TSH and T4 levels at different time points would have enabled greater examination of the precise timing of TSH normalization and disease stabilisation. Medication adherence could also have been investigated during the medical history and by collecting more TSH and T4 information. Also, thyroid hormone concentrations are known to affect cognitive functioning; however we did not obtain thyroid function tests at the time of assessment. Furthermore, we did not collect any biological endocrine data from the control group. Second, our sample size was small. However, this reflects the inclusion criteria for the CH participants as only those with the most severe disease at diagnosis were included. This in itself, whilst enabling the study of the residual deficits which occur despite early identification and treatment of CH, may not reflect the majority of children diagnosed with CH, who often present with a milder form of the condition. Future studies should look to

evaluate children with less severe forms of CH with the methods described. Third, on average, the control group performed above the population mean on Performance IQ and core language. This is in common with other studies of this sort, where participants must volunteer and also travel to the hospital for testing. The majority of control participants were children of university or hospital staff and therefore may be expected to score more highly on these tests compared with the general population. However, differences in Performance IQ were controlled for where possible in order to try and mitigate these effects. Fourth, as highlighted above, whilst as a group, children with CH scored close to the population mean for both performance IQ and core language, this may mask poor performance due to the use of historical normative data which was standardized some time ago and is therefore vulnerable to upward drift. Fifth, the test battery was limited mostly to hearing, language, and communication measures given that these were the main focus of the study. Finally, more detailed matching for socioeconomic status, for example, based on parental education level and income, would have helped to determine whether children with CH were failing to attain their full potential or whether they were performing well considering their early hypothyroidism.

5. Conclusion

To our knowledge, this is the first study to show abnormalities in white matter microstructure using diffusion MRI in children with severe, early treated CH. These results show that, despite early identification and treatment, children with a history of severe CH owing to agenesis of the thyroid gland or complete thyroid dyshormonogenesis, showed significant structural abnormalities in their white matter tracts. Furthermore, microstructural abnormalities were associated with speech-in-noise and core language metrics. Advanced diffusion models that measure fiber dispersion showed that peripheral white matter dispersion correlated with auditory and communication abilities in this group. Finally, while the majority of children with severe CH had functional hearing, language, and communication abilities that were within the normal range, a significant minority (between 16 and 41% depending on the task) did not. Our findings therefore suggest that despite early detection and treatment, infants with severe CH may be at risk of developing white matter microstructural abnormalities which, in a subset of children, correspond to clinically significant hearing, language and communication difficulties in later childhood and adolescence. This highlights the need to ensure optimal early treatment and adequate long-term follow up for children born with severe CH, including assessment of hearing, language, and communication abilities, to enable early intervention where required.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101980.

Acknowledgements

We would like to thank all the children who participated in this study, as well as the radiographers at Great Ormond Street Hospital for their help with MRI acquisitions. We would also like to thank Kiran Seunarine and Jonathan Clayden for their help with MR and statistical analyses. We are grateful to two anonymous reviewers whose comments and suggestions helped improve and clarify this manuscript.

This work was supported by a NIHR/CSO Healthcare Science Doctoral Research Fellowship, Hannah Cooper, NIHR-HCS-D12-03-05. We also acknowledge funding from the NIHR Biomedical Research Centre at Great Ormond Street Hospital and the Great Ormond Street Institute of Child Health, University College London, as well as at University College London Hospitals. Enrico Kaden was supported by grants UK EPSRCEP/M020533/1, EP/N018702/1 and EU H2020 634541-2.

Conflict of interest statement

Hannah Cooper – Reports no disclosures.
Enrico Kaden – Reports no disclosures.
Lorna Halliday – Reports no disclosures.
Doris-Eva Bamiou – Reports no disclosures.
Kshitij Mankad – Reports no disclosures.
Catherine Peters – Reports no disclosures.
Christopher Clark – Reports no disclosures.

References

Albert, B.B., Heather, N., Derraik, J.G., Cutfield, W.S., Wouldes, T., Tregurtha, S., ... Hofman, P.L., 2013. Neurodevelopmental and body composition outcomes in children with congenital hypothyroidism treated with high-dose initial replacement and close monitoring. J. Clin. Endocrinol. Metab. 98 (9), 3663–3670. https://doi.org/10.1210/jc.2013-1903.

Aleksander, P.E., Bruckner-Spieler, M., Stoehr, A.M., Lankes, E., Kuhnen, P., Schnabel, D., Krude, H., 2018. Mean high-dose l-thyroxine treatment is efficient and safe to achieve a Normal IQ in young adult patients with congenital hypothyroidism. J. Clin. Endocrinol. Metab. 103 (4), 1459–1469. https://doi.org/10.1210/jc.2017-01937.

Alm, J., Hagenfeldt, L., Larsson, A., Lundberg, K., 1984. Incidence of congenital hypothyroidism: retrospective study of neonatal laboratory screening versus clinical symptoms as indicators leading to diagnosis. Br. Med. J. (Clin. Res. Ed.) 289 (6453), 1171–1175.

Alvarez, M., Carvajal, F., Renon, A., Perez, C., Olivares, A., Rodriguez, G., Alvarez, V., 2004. Differential effect of fetal, neonatal and treatment variables on neurodevelopment in infants with congenital hypothyroidism. Horm. Res. 61 (1), 17–20. https://doi.org/10.1159/000075192.

Andersson, J.L.R., Sotiropoulos, S.N., 2016. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage 125, 1063–1078. https://doi.org/10.1016/j.neuroimage.2015.10.019.

Andersson, J.L.R., Skare, S., Ashburner, J., 2003. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. Neuroimage 20 (2), 870–888. https://doi.org/10.1016/s1053-8119(03)00336-7.

Bakhtiari, R., Zürcher, N.R., Rogier, O., Russo, B., Hippolyte, L., Granziera, C., Hadjikhani, N., 2012. Differences in white matter reflect atypical developmental trajectory in autism: a tract-based spatial statistics study. Neuroimage Clin 1 (1), 48–56. https://doi.org/10.1016/j.nicl.2012.09.001.

Balazs, R., Brooksbank, B.W., Davison, A.N., Eayrs, J.T., Wilson, D.A., 1969. The effect of neonatal thyroidectomy on myelination in the rat brain. Brain Res. 15 (1), 219–232.

Baldo, J.V., Paulraj, S.R., Curran, B.C., Dronkers, N.F., 2015. Impaired reasoning and problem-solving in individuals with language impairment due to aphasia or language delay. Front. Psychol. 6 (1523). https://doi.org/10.3389/fpsyg.2015.01523.

Bargagna, S., Canepa, G., Costagli, C., Dinetti, D., Marcheschi, M., Millepiedi, S., Chiovato, L., 2000. Neuropsychological follow-up in early-treated congenital hypothyroidism: a problem-oriented approach. Thyroid 10 (3), 243–249. https://doi.org/10.1089/thy.2000.10.243.

Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., Reiss, A.L., 2005. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. Cereb. Cortex 15 (12), 1848–1854. https://doi.org/10.1093/cercor/bhi062.

Barradas, P.C., Vieira, R.S., De Freitas, M.S., 2001. Selective effect of hypothyroidism on expression of myelin markers during development. J. Neurosci. Res. 66 (2), 254–261. https://doi.org/10.1002/jnr.1218.

Basser, P.J., Pierpaoli, C., 1996. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J. Magn. Reson. Ser. B 111 (3), 209–219.

Bernal, J., 2002. Action of thyroid hormone in brain. J. Endocrinol. Investig. 25 (3), 268–288.

Bernal, J., Nunez, J., 1995. Thyroid hormones and brain development. European Journal of Endocrinology of the European Federation of Endocrine Societies 133 (4), 390–398.

Bishop, D.V., 2003. The Children's Communication Checklist, Version 2. Pearson Assessment, London, UK.

Blasi, V., Longaretti, R., Giovanettoni, C., Baldoli, C., Pontesilli, S., Vigone, C., Weber, G., 2009. Decreased parietal cortex activity during mental rotation in children with congenital hypothyroidism. Neuroendocrinology 89 (1), 56–65. https://doi.org/10.1159/000151397.

Bolia, R.S., Nelson, W.T., Ericson, M.A., Simpson, B.D., 2000. A speech corpus for multitalker communications research. J. Acoust. Soc. Am. 107 (2), 1065–1066.

Bongers-Schokking, J.J., Resing, W.C., de Rijke, Y.B., de Ridder, M.A., de Muinck Keizer-Schrama, S.M., 2013. Cognitive development in congenital hypothyroidism: is overtreatment a greater threat than undertreatment? J. Clin. Endocrinol. Metab. 98 (11), 4499–4506. https://doi.org/10.1210/jc.2013-2175.

British Society of Audiology, 2011. Pure-Tone Air-Conduction and Bone-Conduction Threshold Audiometry with and without Masking.

Brungart, D.S., 2001. Informational and energetic masking effects in the perception of two simultaneous talkers. J. Acoust. Soc. Am. 109 (3), 1101–1109.

Bruno, R., Aversa, T., Catena, M., Valenzise, M., Lombardo, F., De Luca, F., Wasniewska, M., 2015. Even in the era of congenital hypothyroidism screening mild and subclinical sensorineural hearing loss remains a relatively common complication of

severe congenital hypothyroidism. Hear. Res. 327, 43–47. https://doi.org/10.1016/j.heares.2015.04.018.
Clairman, H., Skocic, J., Lischinsky, J.E., Rovet, J.F., 2015. Do children with congenital hypothyroidism exhibit abnormal cortical morphology? Pediatr. Res. 78 (3), 286–297. https://doi.org/10.1038/pr.2015.93.
Clayden, J.D., Maniega, S.M., Storkey, A.J., King, M.D., Bastin, M.E., Clark, C.A., 2011. TractoR: magnetic resonance imaging and tractography with R. J. Stat. Softw. 44 (8), 1–18.
Clayden, J.D., Jentschke, S., Munoz, M., Cooper, J.M., Chadwick, M.J., Banks, T., Vargha-Khadem, F., 2012. Normative development of white matter tracts: similarities and differences in relation to age, gender, and intelligence. Cereb. Cortex 22 (8), 1738–1747. https://doi.org/10.1093/cercor/bhr243.
Crandell, C.C., Smaldino, J.J., 2000. Classroom acoustics for children with Normal hearing and with hearing impairment. Lang Speech Hear Serv Sch 31 (4), 362–370. https://doi.org/10.1044/0161-1461.3104.362.
Deoni, S.C., Dean 3rd, D.C., O'Muircheartaigh, J., Dirks, H., Jerskey, B.A., 2012. Investigating white matter development in infancy and early childhood using myelin water faction and relaxation time mapping. Neuroimage 63 (3), 1038–1053. https://doi.org/10.1016/j.neuroimage.2012.07.037.
Donaldson, M., Jones, J., 2013. Optimising outcome in congenital hypothyroidism; current opinions on best practice in initial assessment and subsequent management. J. Clin. Res. Pediatr. Endocrinol. 5 (Suppl. 1), 13–22. https://doi.org/10.4274/jcrpe.849.
Farah, R., Schmithorst, V.J., Keith, R.W., Holland, S.K., 2014. Altered white matter microstructure underlies listening difficulties in children suspected of auditory processing disorders: a DTI study. Brain Behav 4 (4), 531–543. https://doi.org/10.1002/brb3.237.
Fisher, D.A., 1983. Second international conference on neonatal thyroid screening: progress report. J. Pediatr. 102 (5), 653–654.
Flynn, James R., 1984. The mean IQ of Americans: massive gains 1932 to 1978. Psychol. Bull. 95 (1), 29.
Gejao, M.G., Lamonica, D.A., 2008. Development skills in children with congenital hypothyroidism: focus on communication. Pro Fono 20 (1), 25–30.
Gejao, M.G., Ferreira, A.T., Silva, G.K., Anastacio-Pessan Fda, L., Lamonica, D.A., 2009. Communicative and psycholinguistic abilities in children with phenylketonuria and congenital hypothyroidism. J. Appl. Oral Sci. 17, 69–75 *Suppl*.
Gibbard, C.R., Ren, J., Seunarine, K.K., Clayden, J.D., Skuse, D.H., Clark, C.A., 2013. White matter microstructure correlates with autism trait severity in a combined clinical-control sample of high-functioning adults. Neuroimage Clin 3, 106–114. https://doi.org/10.1016/j.nicl.2013.07.007.
Griffiths, P., Griffiths, W., Goddard, P., Scott, E., Tetlow, L., 2014. A laboratory guide to newborn screening in the UK for congenital hypothyroidism. In: N. N. B. S. S. Programme.
Hall, A.J., Midgley, E., Steer, C., Humphriss, R., 2011. Prevalence and risk factors for mild and high-frequency bilateral sensorineural hearing loss at age 11 years old: a UK prospective cohort study. Int. J. Audiol. 50 (11), 809–814. https://doi.org/10.3109/14992027.2011.599869.
Hamada, T., Iwaki, S., Kawano, T., 2004. Speech offsets activate the right parietal cortex. Hear. Res. 195 (1–2), 75–78. https://doi.org/10.1016/j.heares.2004.04.013.
Hulse, J.A., 1984. Outcome for congenital hypothyroidism. Arch. Dis. Child. 59 (1), 23–29.
Jenkinson, M., Beckmann, C.F., Behrens, T.E., Woolrich, M.W., Smith, S.M., 2012. FSL. Neuroimage 62 (2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015.
Kaden, E., Kelm, N.D., Carson, R.P., Does, M.D., Alexander, D.C., 2016a. Multi-compartment microscopic diffusion imaging. Neuroimage. https://doi.org/10.1016/j.neuroimage.2016.06.002.
Kaden, E., Kruggel, F., Alexander, D.C., 2016b. Quantitative mapping of the per-axon diffusion coefficients in brain white matter. Magn. Reson. Med. 75 (4), 1752–1763. https://doi.org/10.1002/mrm.25734.
Knowles, R.L., 2011. UK Surveillance of Primary Congenital Hypothyroidism in Children Aged Five Years and under (UKCHT).
Kopp, P., van Sande, J., Parma, J., Duprez, L., Gerber, H., Joss, E., ... Vassart, G., 1995. Brief report: congenital hyperthyroidism caused by a mutation in the thyrotropin-receptor gene. N. Engl. J. Med. 332 (3), 150–154. https://doi.org/10.1056/nejm199501193320304.
Lee, J.C., Nopoulos, P.C., Tomblin, J.B., 2013. Abnormal subcortical components of the corticostriatal system in young adults with DLI: a combined structural MRI and DTI study. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2013.07.011.
Levitt, H., 1971. Transformed up-down methods in psychoacoustics. J. Acoustical Society of Am. 49(2) (Suppl. 2), 467.
Lichtenberger-Geslin, L., Dos Santos, S., Hassani, Y., Ecosse, E., Van Den Abbeele, T., Leger, J., 2013. Factors associated with hearing impairment in patients with congenital hypothyroidism treated since the neonatal period: a national population-based study. J. Clin. Endocrinol. Metab. 98 (9), 3644–3652. https://doi.org/10.1210/jc.2013-1645.
Messaoud-Galusi, S., Hazan, V., Rosen, S., 2011. Investigating speech perception in children with dyslexia: is there evidence of a consistent deficit in individuals? J. Speech, Language, Hearing Res. 54 (6), 1682–1701. https://doi.org/10.1044/1092-4388(2011/09-0261).
Mitchell, M.L., Hsu, H.W., Sahai, I., 2011. The increased incidence of congenital hypothyroidism: fact or fancy? Clin. Endocrinol. 75 (6), 806–810. https://doi.org/10.1111/j.1365-2265.2011.04128.x.
Murner-Lavanchy, I.M., Kelly, C.E., Reidy, N., Doyle, L.W., Lee, K.J., Inder, T., Anderson, P.J., 2018. White matter microstructure is associated with language in children born very preterm. Neuroimage Clin 20, 808–822. https://doi.org/10.1016/j.nicl.2018.09.020.
Nagayama, J., Kohno, H., Kunisue, T., Kataoka, K., Shimomura, H., Tanabe, S., Konishi, S., 2007. Concentrations of organochlorine pollutants in mothers who gave birth to neonates with congenital hypothyroidism. Chemosphere 68 (5), 972–976. https://doi.org/10.1016/j.chemosphere.2007.01.010.
Noble, M., McLennan, D., Wilkinson, K., Whitworth, A., Exley, S., Barnes, H., McLennan, D., 2007. The English Indices of Deprivation. pp. 2007.
Norbury, C.F., Nash, M., Baird, G., Bishop, D., 2004. Using a parental checklist to identify diagnostic groups in children with communication impairment: a validation of the Children's communication checklist–2. Int. J. Language Comm. Dis. 39 (3), 345–364. https://doi.org/10.1080/13682820410001654883.
Norbury, C.F., Gooch, D., Wray, C., Baird, G., Charman, T., Simonoff, E., ... Pickles, A., 2016. The impact of nonverbal ability on prevalence and clinical presentation of language disorder: evidence from a population study. J. Child Psychol. Psychiatry Allied Discip. 57 (11), 1247–1257. https://doi.org/10.1111/jcpp.12573.
Oerbeck, B., Sundet, K., Kase, B.F., Heyerdahl, S., 2005. Congenital hypothyroidism: no adverse effects of high dose thyroxine treatment on adult memory, attention, and behavior. Arch. Dis. Child. 90 (2), 132–137. https://doi.org/10.1136/adc.2003.043935.
Oerbeck, B., Reinvang, I., Sundet, K., Heyerdahl, S., 2007. Young adults with severe congenital hypothyroidism: cognitive event related potentials (ERPs) and the significance of an early start of thyroxine treatment. Scand. J. Psychol. 48 (1), 61–67. https://doi.org/10.1111/j.1467-9450.2006.00545.x.
Owen, J.P., Marco, E.J., Desai, S., Fourie, E., Harris, J., Hill, S.S., Mukherjee, P., 2013. Abnormal white matter microstructure in children with sensory processing disorders. Neuroimage Clin 2, 844–853. https://doi.org/10.1016/j.nicl.2013.06.009.
Prezioso, G., Giannini, C., Chiarelli, F., 2018. Effect of thyroid hormones on neurons and neurodevelopment. Hormone Res. Pediatr. 90 (2), 73–81. https://doi.org/10.1159/000492129.
Qiu, D., Tan, L.H., Zhou, K., Khong, P.L., 2008. Diffusion tensor imaging of normal white matter maturation from late childhood to young adulthood: voxel-wise evaluation of mean diffusivity, fractional anisotropy, radial and axial diffusivities, and correlation with reading development. Neuroimage 41 (2), 223–232. https://doi.org/10.1016/j.neuroimage.2008.02.023.
Rachmiel, M., Blaser, S., Widjaja, E., Rovet, J.F., 2013. Children with congenital hypothyroidism have similar neuroradiological abnormal findings as healthy ones. ScientificWorldJournal 2013, 194918. https://doi.org/10.1155/2013/194918.
Rastogi, M.V., LaFranchi, S.H., 2010. Congenital hypothyroidism. Orphanet J. Rare Dis. 5 (17). https://doi.org/10.1186/1750-1172-5-17.
Rovet, J.F., 1999a. Congenital hypothyroidism: long-term outcome. Thyroid 9 (7), 741–748.
Rovet, J.F., 1999b. Long-term neuropsychological sequelae of early-treated congenital hypothyroidism: effects in adolescence. Acta Pediatrica. Supplement 88 (432), 88–95.
Rovet, J.F., 2014. The role of thyroid hormones for brain development and cognitive function. Endocr. Dev. 26, 26–43. https://doi.org/10.1159/000363153.
Rovet, J.F., Ehrlich, R.M., 1995. Long-term effects of L-thyroxine therapy for congenital hypothyroidism. J. Pediatr. 126 (3), 380–386.
Rovet, J.F., Ehrlich, R.M., Sorbara, D.L., 1989. Effect of thyroid hormone level on temperament in infants with congenital hypothyroidism detected by screening of neonates. J. Pediatr. 114 (1), 63–68.
Rovet, J.F., Ehrlich, R.M., Sorbara, D.L., 1992. Neurodevelopment in infants and preschool children with congenital hypothyroidism: etiological and treatment factors affecting outcome. J. Pediatr. Psychol. 17 (2), 187–213.
Rovet, J.F., Walker, W., Bliss, B., Buchanan, L., Ehrlich, R., 1996. Long-term sequelae of hearing impairment in congenital hypothyroidism. J. Pediatr. 128 (6), 776–783.
Schmahmann, J. D., Pandya, D. N., Wang, R., Dai, G., D'Arceuil, H. E., de Crespigny, A. J., & Wedeen, V. J. (2007). Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. Brain, 130(Pt 3), 630–653. https://doi.org/10.1093/brain/awl359.
Schmithorst, V.J., Wilke, M., Dardzinski, B.J., Holland, S.K., 2002. Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study. Radiology 222 (1), 212–218. https://doi.org/10.1148/radiol.2221010626.
Schmithorst, V.J., Wilke, M., Dardzinski, B.J., Holland, S.K., 2005. Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. Hum. Brain Mapp. 26 (2), 139–147. https://doi.org/10.1002/hbm.20149.
Schmithorst, V.J., Holland, S.K., Plante, E., 2011. Diffusion tensor imaging reveals white matter microstructure correlations with auditory processing ability. Ear Hear. 32 (2), 156–167. https://doi.org/10.1097/AUD.0b013e3181f7a481.
Semel, E., Wiig, E.H., Secord, W.A., 2003. Clinical Evaulation of Language Fundamentals - Fourth Edition UK (CELF-4 UK). Pearson Assessment, London, UK.
Seunarine, K.K., Clayden, J.D., Jentschke, S., Munoz, M., Cooper, J.M., Chadwick, M.J., Clark, C.A., 2016. Sexual dimorphism in white matter developmental trajectories using tract-based spatial statistics. Brain Connect 6 (1), 37–47. https://doi.org/10.1089/brain.2015.0340.
Sharlin, D.S., Tighe, D., Gilbert, M.E., Zoeller, R.T., 2008. The balance between oligodendrocyte and astrocyte production in major white matter tracts is linearly related to serum total thyroxine. Endocrinology 149 (5), 2527–2536. https://doi.org/10.1210/en.2007-1431.
Simic, N., Rovet, J.F., 2016. Dorsal and ventral visual streams: typical and atypical development. Child Neuropsychol. 1–14. https://doi.org/10.1080/09297049.2016.1186616.
Siragusa, V., Boffelli, S., Weber, G., Triulzi, F., Orezzi, S., Scotti, G., Chiumello, G., 1997. Brain magnetic resonance imaging in congenital hypothyroid infants at diagnosis. Thyroid 7 (5), 761–764.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17 (3),

143–155. https://doi.org/10.1002/hbm.10062.
Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., ... Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 (Suppl. 1), S208–S219. https://doi.org/10.1016/j.neuroimage.2004.07.051.
Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Behrens, T.E., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage 31 (4), 1487–1505. https://doi.org/10.1016/j.neuroimage.2006.02.024.
Song, S.I., Daneman, D., Rovet, J.F., 2001. The influence of etiology and treatment factors on intellectual outcome in congenital hypothyroidism. J. Dev. Behav. Pediatr. 22 (6), 376–384.
Song, S.K., Sun, S.W., Ju, W.K., Lin, S.J., Cross, A.H., Neufeld, A.H., 2003. Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage 20 (3), 1714–1722.
Verhoeven, J.S., Rommel, N., Prodi, E., Leemans, A., Zink, I., Vandewalle, E., Sunaert, S., 2012. Is there a common neuroanatomical substrate of language deficit between autism spectrum disorder and specific language impairment? Cereb. Cortex 22 (10), 2263–2271. https://doi.org/10.1093/cercor/bhr292.
Wechsler, D., 1999. *Wechsler abbreviated scale of intelligence*: Psychological Corporation.
Wheeler, S.M., Willoughby, K.A., McAndrews, M.P., Rovet, J.F., 2011. Hippocampal size and memory functioning in children and adolescents with congenital hypothyroidism. J. Clin. Endocrinol. Metab. 96 (9), E1427–E1434. https://doi.org/10.1210/jc.2011-0119.
Wheeler, S.M., McLelland, V.C., Sheard, E., McAndrews, M.P., Rovet, J.F., 2015. Hippocampal functioning and verbal associative memory in adolescents with congenital hypothyroidism. Front. Endocrinol. 6 (163). https://doi.org/10.3389/fendo.2015.00163.
Zoeller, R.T., Rovet, J.F., 2004. Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. J. Neuroendocrinol. 16 (10), 809–818. https://doi.org/10.1111/j.1365-2826.2004.01243.x.