NeuroImage: Clinical 17 (2018) 899–909

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Grey matter volume and cortical structure in Prader-Willi syndrome compared to typically developing young adults

Katherine E. Manning[a,*], Roger Tait[a], John Suckling[a], Anthony J. Holland[a,b,c]

[a] Department of Psychiatry, University of Cambridge, Cambridge, UK
[b] Cambridgeshire and Peterborough NHS Foundation Trust, UK
[c] National Institute for Health Research (NIHR) Collaborations for Leadership in Applied Health Care Research and Care (CLAHRC), East of England, UK

ARTICLE INFO

Keywords:
Prader-Willi syndrome
Grey matter
Multiparameter mapping
Myelination
Cortical thickness
Genomic imprinting

ABSTRACT

Prader-Willi syndrome (PWS) is a neurodevelopmental disorder of genomic imprinting, presenting with a characteristic overeating disorder, mild to moderate intellectual disability, and a variable range of social and behavioral difficulties. Consequently, widespread alterations in neural structure and developmental and maturational trajectory would be expected. To date, there have been few quantitative and systematic studies of brain morphology in PWS, although alterations of volume and of cortical organisation have been reported. This study aimed to investigate, in detail, the structure of grey matter and cortex in the brain in a sample of young adults with PWS in a well-matched case-controlled analysis. 20 young adults with PWS, aged 19–27 years, underwent multiparameter mapping magnetic resonance imaging sequences, from which measures of grey matter volume, cortical thickness and magnetisation transfer saturation, as a proxy measure of myelination, were examined. These variables were investigated in comparison to a control group of 40 typically developing young adults, matched for age and sex. A voxel-based morphometry analysis identified large and widespread bilateral clusters of both increased and decreased grey matter volume in the brain in PWS. In particular, widespread areas of increased volume encompassed parts of the prefrontal cortex, especially medially, the majority of the cingulate cortices, from anterior to posterior aspects, insula cortices, and areas of the parietal and temporal cortices. Increased volume was also reported in the caudate, putamen and thalamus. The most ventromedial prefrontal areas, in contrast, showed reduced volume, as did the parts of the medial temporal lobe, bilateral temporal poles, and a small cluster in the right lateral prefrontal cortex. Analysis of cortical structure revealed that areas of increased volume in the PWS group were largely driven by greater cortical thickness. Conversely, analysis of myelin content using magnetisation transfer saturation indicated that myelination of the cortex was broadly similar in the PWS and control groups, with the exception of highly localised areas, including the insula. The bilateral nature of these abnormalities suggests a systemic biological cause, with possible developmental and maturational mechanisms discussed, and may offer insight into the contribution of imprinted genes to neural development.

1. Introduction

Prader-Willi syndrome (PWS) is a neurodevelopmental disorder affecting around 1 in 25,000–29,000 births (Whittington et al., 2001; Smith et al., 2003). PWS arises due to the evolutionary phenomenon of gender of origin specific genomic imprinting, whereby specific genes are programmed to be silent or expressed according to the chromosome's maternal or paternal origin. In PWS there is a failure of paternal expression of maternally imprinted genes at chromosomal locus 15q11-13 (the PWS critical region), with almost all cases accounted for by one of three genetic events: deletion of the critical region on the paternal chromosome (c. 70%); maternal uniparental disomy of chromosome 15 (UPD; c. 25%); or an imprinting centre defect (< 5%) (Bittel and Butler, 2005). The common result of all genetic causes is the loss of expression of the paternal alleles of maternally imprinted genes in this critical region.

PWS presents with a characteristic, although variable, profile (Holm et al., 1993). Most prominently, infants are born with severe hypotonia (low muscle tone) and show an initial failure to thrive, which is replaced during preschool years by an insatiable appetite, necessitating

Abbreviations: ANTS, Advanced Normalisation Tools Software; ACC, anterior cingulate cortex; BMI, body mass index; CamBA, Cambridge Brain Analysis software; TE, echo time; FA, flip angle; GLM, general linear model; GM, grey matter; IQ, intelligence quotient; MRI, magnetic resonance imaging; MPM, multiparameter mapping; MT, magnetisation transfer; NHS, National Health Service; NSPN, NeuroScience in Psychiatry Network; OFC, orbitofrontal cortex; PWS, Prader-Willi syndrome; PWSA UK, Prader-Willi Syndrome Association UK; PFC, prefrontal cortex; PD, proton density; TR, repetition time; TIV, total intracranial volume; UPD, uniparental disomy; WM, white matter

* Corresponding author at: CIDDRG, Department of Psychiatry, University of Cambridge, Douglas House, 18b Trumpington Road, Cambridge CB2 8AH, UK.
E-mail address: kem60@medschl.cam.ac.uk (K.E. Manning).

https://doi.org/10.1016/j.nicl.2017.12.027
Received 30 October 2017; Received in revised form 14 December 2017; Accepted 19 December 2017
Available online 20 December 2017
2213-1582/ © 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

external restriction of food and commonly resulting in life-threatening obesity if such restrictions are not in place. Relative growth and sex hormone deficiencies mean that short stature is common, sexual development is disrupted, and a typical facial phenotype is often present. These characteristics strongly suggest a disorder of hypothalamic control. However, beyond these core features, PWS is also associated with mild to moderate intellectual disability, a high pain threshold and a variable range of social and behavioral difficulties, including temper outbursts, need for routine, skin picking, repetitive and ritualistic behaviours, and poor social functioning, as well as propensity to psychiatric disturbance (Dykens and Kasari, 1997; Clarke et al., 2002; Holland et al., 2003).

These diverse phenotypic effects indicate a widespread atypical pattern of development of the PWS brain. However, whilst the characterisation of PWS at the cognitive and behavioral level has received considerable attention, a recent systematic review highlighted the lack of comprehensive or systematic study and consensus at the neural level (Manning and Holland, 2015), with the notable exception of the eating behavior which has been associated with aberrant central satiety responses (e.g. Hinton et al., 2006; Holsen et al., 2006). In particular, few systematic and quantitative studies of neural morphology in PWS were identified, although a number of case studies and other studies using more qualitative measurement or categorisation of regions of interest have suggested diffuse abnormalities, particularly in frontal and wider cortical regions, when focus was not restricted to the hypothalamic pituitary area. Functional studies also indicate aberrant activity in similar areas, both in response to tasks and resting state, especially implicating regions of the cortico-striatal-thalamic loops involved in cognition, motivation and emotional regulation over behavioral control (e.g. Hinton et al., 2006; Holsen et al., 2006; Kim et al., 2006; Miller et al., 2007; Woodcock et al., 2010). Considering quantitative structural investigations of grey matter (GM) in PWS, Ogura et al. (2011) reported reduced total GM volume, and particular reductions in orbitofrontal cortex (OFC) and somatomotor areas, in a voxel-based morphometry (VBM) study comparing 12 participants with PWS to age and sex-matched control participants. Abnormal cortical gyrification with reduced cortical complexity particularly in frontal areas, including the insula and cingulate regions, as well as in parietal and temporal cortices has also been reported, alongside reduced total cortical surface area in children with PWS compared to sibling controls (Lukoshe et al., 2013; Lukoshe et al., 2014). Most recently, Xu et al. (2017) reported reduced total cortical volume and reductions in the medial prefrontal cortex (PFC), dorsolateral PFC, right anterior cingulate cortex (ACC) and in temporal and occipital areas in children with PWS compared to healthy controls, however these alterations were also seen in a highly obese group.

Given the few systematic and quantitative investigations of the PWS brain, this analysis aims to explore neuroanatomy at the level of a whole brain exploratory analysis. Voxel-based morphometry analyses enable comparison of GM volume across the whole brain in different populations using fully automated processes. In addition to investigating GM volume in PWS, this study also considers cortical structure and, in particular, how cortical structure may be involved in differences in GM volume. The aim of this study was to address the paucity of systematic and quantitative investigations into the structure of the brain in vivo in PWS cross-sectionally compared to a well-matched control group. In doing so, this data-driven analysis approach, unrestricted by anatomical boundaries, conducted within one of the largest PWS neuroimaging cohorts to date and confined to young adults, aims to address a number of the potential confounds implicated in previous conflicting findings.

2. Methods

Ethical approval was granted by the National Health Service (NHS) National Research Ethics Service (13/EE/0373) and relevant NHS and university research and development approvals were obtained.

2.1. Participants

Twenty-six young adults, meeting the study criteria of being aged between 18 and 28 years and with a genetic diagnosis of PWS, were recruited from across England via the Prader-Willi Syndrome Association UK (PWSA UK), residential home providers and NHS clinicians. This represents approximately 14.5% of all adults aged 18–28 years with PWS in England, estimated according to the prevalence known to the PWSA UK. Only those with capacity to consent, assessed in accordance with Section 3 of the UK Mental Capacity Act 2005, were eligible to participate. Of these 26 participants, six failed to complete the magnetic resonance imaging (MRI) assessments. Consequently, the final sample comprised 20 people with PWS.

Forty control participants, matched to the PWS participants for age and sex in a two-to-one fashion, were included in the study. Typically developing participants aged 18–24 years were recruited and tested as part of the NeuroScience in Psychiatry Network (NSPN) U-Change project, enabling the selection of age and sex-matched controls. Control participants aged 24–28 years were additionally recruited from the local population. For sex, matching was possible for all except one male with PWS who was matched to two control females. The majority of participants with PWS were matched with two control participants within six months of their age; the maximum age difference was 2.25 years. It was not possible to match for BMI and IQ owing to the association of PWS with these variables and a characteristic part of how people with PWS typically differ from the typically-developing population.

Exclusion criteria for both groups were standard MRI safety exclusion criteria or inability to tolerate the MRI environment, history of neurological disorder or trauma, and current or recent (within 12 months) participation in a clinical trial of a medicinal product. For the control group, this additionally included current treatment for a psychiatric disorder or drug or alcohol dependence and intellectual disability requiring educational support or treatment. For the PWS group, the presence of a current psychiatric disorder disrupting compliance with study demands also precluded participation.

2.2. Clinical, genetic and cognitive characteristics

History of growth and sex hormone treatment and medications for the PWS group were given by participants with PWS, their parents and carers. For those with PWS, genetic diagnosis of subtype was obtained via medical records where available or confirmed using saliva or blood samples. Height and weight was recorded for all participants at the scan visit.

IQ in the PWS group was assessed via administration of the complete Wechsler Adult Intelligence Scales Fourth Edition (WAIS-IV; Wechsler, 2008). The control group completed only the vocabulary and matrix reasoning subtests from the Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II; Wechsler, 2011), a shortened version of the WAIS.

2.3. Magnetic resonance imaging protocol

Participants underwent an multiparameter mapping sequence (MPM) allowing fast high resolution whole brain T1, T2*, proton density (PD) and magnetisation transfer (MT) mapping, thus assessing parameters sensitive to iron concentration, water content and myelination as well as more traditional anatomical MRI data. As described in more detail by Draganski et al. (2011), the MPM imaging protocol consisted of T1-weighted, PD-weighted and MT-weighted sequence and two field map sequences. The analyses reported here are carried out on the R1 (1/T1) data from the T1-weighted sequence and the MT saturation images from the MT sequence.

Repetition time (TR) was 18.70 ms for the T1-weighted sequence

Download English Version:

https://daneshyari.com/en/article/8688129

Download Persian Version:

https://daneshyari.com/article/8688129

Daneshyari.com