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Midline brain structures in adult Niemann-Pick type C disease: a cross-sectional study

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Abstract

Objective: A range of neuropathological changes occur in the brains of individuals with adult Niemann-Pick type C disease (NPC), a recessive disorder of cholesterol trafficking that results in accumulation of cholesterol and gangliosides in lysosomes, particularly in neurons. One of the most significant regions of grey matter loss occurs in the thalami, which abut the midline. What is not known is whether these are neurodevelopmental in origin well prior to symptomatic onset. We aimed to examine other markers of midline developmental anomalies in adults with NPC. **Method:** We examined the size of adhesio interthalamica (AI) and cavum septum pellucidum (CSP) (if present) in nine individuals diagnosed with NPC and nine healthy comparison subjects, matched for age and gender, using a 3T magnetic resonance volumetric sequence and measured the length of the AI and CSP in mm. **Results:** We found that 5/9 NPC patients and 0/9 controls had a missing AI. AI length was significantly shorter in the patient group. No subject in other group had a large CSP, and CSP length did not differ. Duration of illness showed a trend to a negative correlation with AI length in patients. **Conclusions:** Our findings suggest that adult NPC patients show some markers of early neurodevelopmental disturbance, matching findings seen in psychotic disorders. The differences in AI, but not CSP, suggest neurodevelopmental change may occur early in gestation rather than post-partum. The relationship with duration of illness suggests that there may be atrophy over time in these structures, consistent with prior analyses of grey matter regions in NPC.

Significant outcomes

- Patients with Niemann-Pick type C (NPC) disease have elevated rates of adhesio interthalamica (AI), and when present, it is shorter than controls and correlates inversely with duration of illness.
- There were no differences in size of the cavum septum pellucidum in NPC patients compared to controls.
- This difference suggests that an early rather than late neurodevelopmental disturbance may occur in NPC patients, as may occur in schizophrenia, in addition to accelerated brain atrophy.
- This supports the notion that NPC in adults may have both neurodegenerative and neurodevelopmental components.

Key limitations

- This study was cross-sectional rather than longitudinal.
- The small sample size may limit the capacity to detect true change across both structures.
- Higher resolution imaging may have the power to more sensitively detect change.

Introduction

Niemann-Pick disease type C (NPC) is an autosomal recessive neurometabolic disorder of intracellular cholesterol trafficking caused by a mutation in the *NPC1* or *NPC2* genes

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(Carstea et al., 1997), with a combined estimated prevalence of approximately 1:89,000 live births (Wassif et al., 2016), although more recent studies have suggested that a later-onset phenotype may have a significantly higher incidence of 1/20,000–40,000. The disruption of intracellular cholesterol trafficking results in accumulation of unesterified cholesterol and glycosphingolipids/gangliosides in lysosomes, particularly in the brain, spleen and liver. In children, the disorder presents with neonatal jaundice and splenomegaly, developmental delay, seizures and gelastic cataplexy; in adults, it more commonly presents with ataxia, dystonia, schizophrenia-like psychosis and vertical gaze palsy (Walterfang et al., 2006b; Sévin et al., 2007; Vanier, 2015).

A range of neuropathological changes occur in the brains of individuals with NPC, some of which are common to other lysosomal storage disorders (LSDs), such as meganeurite formation, neuronal distension, axonal swelling and spheroid formation and ectopic dendritogenesis (Walkley & Suzuki, 2004). However, significant overlap occurs with other neurodegenerative disorders, including altered amyloid processing (Arenas et al., 2017), and tauopathy including paired helical filament (PHF)-type neurofibrillary tangles (Suzuki et al., 1995; Love et al., 1995). Brain regions most affected by these pathological changes, and where neuronal loss is greatest, include cerebellum, brainstem, hippocampus, thalamus and basal ganglia most particularly (Walkley et al., 1991); these regions are where the greatest ganglioside excess (Zervas et al., 2001; German et al., 2001), tangle formation (other than the cerebellum) (Love et al., 1995; Suzuki et al., 1995) and neuroinflammation (Pressey et al., 2012) occurs.

Previous neuroimaging studies in adult NPC patients have largely confirmed these changes, suggesting grey matter volume losses occur in these subcortical regions and progress over time (Walterfang et al., 2010; Walterfang et al., 2012; Walterfang et al., 2013; Bowman et al., 2015; Masingue et al., 2017), but are also accompanied by widespread white matter changes (Trouard et al., 2005; Walterfang et al., 2010; Lau et al., 2016; Masingue et al., 2017), particularly affecting midline structures such as the corpus callosum (Trouard et al., 2005; Walterfang et al., 2011; Lee et al., 2014; Masingue et al., 2017), and the most significant atrophy of subcortical grey matter structures is seen in the thalami (Walterfang et al., 2010; Masingue et al., 2017), which abut the midline. These changes have been well described and are largely consistent across studies; however, what is not known is whether these changes arise as a result of pathological changes affecting normally developed brain structures, or whether there are more subtle neurodevelopmental changes that occur in the brains of some adult NPC patients that may then be affected by degenerative change (Rego et al., 2019); many adult patients demonstrate subtle developmental changes in childhood prior to the onset of frank cognitive, neuropsychiatric or motor symptoms during adulthood (Walterfang et al., 2006a; Sévin et al., 2007; Vanier, 2010).

One way of indexing possible early neurodevelopmental change is to examine brain structural changes that have shown to be markers of subtle neurodevelopmental anomalies in other adult brain disorders, particularly neuropsychiatric illness such as schizophrenia, bipolar disorder or major depression. Alterations in the midline structures adhesio interthalamica (AI) and cavum septum pellucidum (CSP) have been shown to be over-represented in these major psychiatric illnesses, two- to threefold, and may represent markers of subtly altered early-life neurodevelopmental trajectory (Trzesniak et al., 2011a; Trzesniak et al., 2011b; Landin-Romero et al., 2016).

The AI, or *massa intermedia*, is a flattened grey matter band which connects the medial surfaces of the thalami across the third ventricle and which generally fuses by the 13th week of gestation (Rosales et al., 1968). The AI varies in size among individuals, absent in about 15–25% of human brains (Samra & Cooper, 1968; Carpenter & Sutin, 1983) and has been suggested as a marker of developmental problems during early gestation. A CSP is formed by the incomplete fusion of the septum pellucidum (Rakic & Yakovlev, 1968), which normally occurs within 5 months of birth, usually due to growth of surrounding structures (Sarwar, 1989). A CSP of <5 mm is common in a large proportion of healthy individuals and may occur in up to 30% of the adult population (Shunk, 1963). An enlarged CSP (≥ 6 mm) (Takahashi et al., 2007) is often associated with developmental anomalies of the corpus callosum (Rakic & Yakovlev, 1968; Shen et al., 2015) and alterations in limbic structures such as hippocampus and thalamus (Dremmen et al., 2019), suggesting neurodevelopmental changes occurring when midline and limbic structures are developing during gestation (Wright et al., 1995). Limbic structures have been reported to show, at least cross-sectionally, significant volumetric reductions in adult patients compared to controls (Walterfang et al., 2010; Walterfang et al., 2013), but the timing of these changes has not yet been examined.

In this study, we sought to examine these mid-line structures in a cohort of well-defined adult NPC patients utilising magnetic resonance imaging. We predicted that NPC patients would show an increased incidence of a missing AI, have a shorter AI, and have a larger CSP.

Methods

Standard protocol approvals, registrations and patient consent

The study was approved by the Melbourne Health ethics committee (approval: 2012.066), and all participants provided written informed consent.

Participants

A total of 18 participants were included in this study, including 9 individuals diagnosed with Niemann-Pick disease type C (NPC) and 9 healthy comparison subjects. Healthy controls were selected from a previous study (Di Biase et al., 2017) based on one-to-one age and gender matching with NPC patients. Participant characteristics are shown in Table 1.

Eligible patients were diagnosed with NPC with initial biochemical testing using filipin staining, with follow-up confirmation via NPC1 genotyping. Exclusion criteria for all participants included a history of head injury, impaired thyroid functioning, diabetes, pregnancy or any contraindication to MRI scanning. Patients' duration of neurological symptoms was used as a duration of illness (DOI) measure. Additional exclusion criteria for healthy controls, recruited through advertisement, were a history of neurologic or mental illness (personally or in a first degree relative) or alcohol or drug dependence. Healthy controls were interviewed by two trained investigators using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First & Gibbon, 2004) to confirm they had no history of diagnosable psychopathology.

Table 1. Sample population and main measures

	HC		NPC			
Male/female	4/5		4/5			
	M	SD	M	SD	t/F	p
Age	32	9	32	12	0.07	0.94
BMI	26.9	5.8	24	4.7	−1.16	0.26
DOI (years)			9	3		
AI presence	9/9		4/9			
AI length	12.8	2.7	3.2	2.6	28.31	<0.001
Large CSP	0/9		0/9			
CSP length	2.2	1.2	1.3	1.2	1.30	0.30

HC, healthy control; NPC, Niemann-Pick disease type C; BMI, body mass index; M, mean; SD, standard deviation; t, t statistic; p, p-value. Equal variances not assumed.

Clinical measures

The following scales were administered within one week of scanning: the SCID (First & Gibbon, 2004) to confirm exclusion criteria for healthy controls and the Iturriaga rating scale (Iturriaga *et al.*, 2006) to measure illness severity in NPC patients.

Magnetic Resonance Imaging (MRI) acquisition

T1-weighted and MRI scans were acquired in each participant with a 3-T Siemens Trio at the Murdoch Children's Research Institute, Royal Children's Hospital, Parkville Victoria. For T1-weighted images, scanning parameters were as follows: 3D SPGR spoiled gradient T1 weighted, echo time = 3 ms, repetition time = 14 ms, 256 contiguous slices covering whole brain, $1 \times 1 \times 1$ mm voxels. T1-weighted sequences were repeated if images were affected by movement, as determined by the radiologist.

Measurement of structural volumes

To assess the AI and CSP, the images were processed using Dr View software (AJS, Tokyo, Japan) as described previously (Takahashi *et al.*, 2007; Takahashi *et al.*, 2008a; Takahashi *et al.*, 2008b; Takahashi *et al.*, 2008c; Takahashi *et al.*, 2008d; Takahashi *et al.*, 2008e; Takahashi *et al.*, 2009). Briefly, brain images were realigned in three dimensions and then reconstructed into entire contiguous coronal images with a 1-mm thickness, perpendicular to the anterior commissure-posterior commissure (AC-PC) line. One rater (TT), who was blind to the subjects' identity and time of scan, counted the number of coronal slices where each midline region was clearly seen. The length of the AI and CSP (in mm) was equal to the number of these slices. We considered the AI as present when it could be identified on three or more slices on both coronal and axial views (Takahashi *et al.*, 2008a). A CSP equal to or greater than 6 mm was defined as large on the basis of previous analyses (Takahashi *et al.*, 2008a; Takahashi *et al.*, 2008c; Takahashi *et al.*, 2008d). Examples of findings from this sample are shown in Fig. 1. Intra- and inter-rater (TT, DS) intraclass correlation coefficients were high for the AI (intra-rater 0.935, inter-rater 0.908) and for the CSP (intra-rater 0.994, inter-rater 0.996).

Statistical analyses

Between-group differences

Fisher's exact tests (for cell sizes <5) were used to assess the frequency of the AI and a large CSP. The length of each midline

region, which followed a normal distribution (tested by Shapiro-Wilk test), was analyzed using analysis of variance (ANOVA).

Correlations between AI/CSP length and illness measures

The relationships between the midline regions and clinical variables (DOI, illness severity) were examined by Pearson's partial correlation coefficients controlling for age. DOI and illness severity were normally distributed (Shapiro-Wilk test).

Results

Between-group comparisons

Compared to healthy controls, NPC patients had a missing AI in 5/9 (Table 1, sTable 1), with no control showing a missing AI (Fisher's exact test, $p < 0.05$). No patient nor control had a large CSP however. AI length was significantly shorter in the NPC patient group ($p < 0.001$), but CSP length did not differ between the groups ($p = 0.152$). These results did not change even when we used non-parametric Mann-Whitney U tests (AI length, $U = 0.0$, $p < 0.001$; CSP length, $U = 24.5$, $p = 0.161$).

Correlations

Illness severity did not correlate with CSP ($p = 0.975$) nor AI ($p = 0.992$) length; duration of illness showed no correlation with CSP length ($p = 0.198$) but did show a trend to a negative correlation with AI length ($p = 0.09$).

Discussion

We have demonstrated that adult NPC patients have an elevated rate of an absent AI and a shorter AI compared to matched controls. This is similar to findings seen in first episode and high-risk subjects with schizophrenia, where it has been suggested a shorter or more often absent AI represents an early neurodevelopmental disturbance (Takahashi *et al.*, 2008c; Takahashi *et al.*, 2008d; Trzesniak *et al.*, 2011a). However, we did not identify differences in CSP measures, suggesting that this midline structure may not be a significant marker for any neurodevelopmental disruption in NPC.

Although this was not a longitudinal analysis, the trend towards a correlation between duration of illness and the AI length suggests that this structure may atrophy with time. It has been demonstrated that the AI can show atrophy in both schizophrenia patients and controls (Trzesniak *et al.*, 2012; Takahashi *et al.*, 2013), and it may be

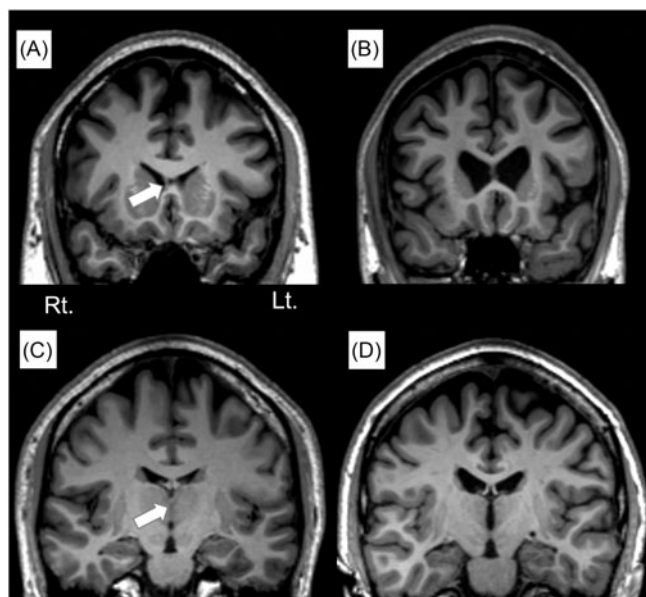


Figure 1. Sample coronal views of the T1-weighted MR images in subjects with (A) and without (B) the cavum septum pellucidum (CSP) and in those with (C) and without (D) the adhesion interthalamica (AI). Arrows indicate the position of each midline brain structure.

a similar process that occurs in adult NPC patients as the AI develops early in gestation but shows some involution with brain ageing (Rosales *et al.*, 1968). It is known that the midline nuclei of the thalamus, including the AI, have efferent connections to the amygdaloid nuclei (Graff-Radford, 1997), and patients with schizophrenia without an AI show smaller amygdaloid volumes (Takahashi *et al.*, 2008a), suggesting that an absent AI could be a marker of neurodevelopmental disruptions to limbo-thalamic circuitry. It is possible that the trend relationship to illness severity may be a marker of accelerated atrophy in NPC, although longitudinal data are required to confirm this finding.

The lack of findings in the CSP suggest that, if altered early-life neurodevelopment occurs in patients who are diagnosed with NPC in adulthood, it has its impact during the early intra-gestational period when the AI is forming, but not later when the septum pellucidum fuse post-partum. A similar discrepancy between AI and CSP findings – with the former but not latter disrupted – has been shown in major neuropsychiatric disorders such as bipolar disorder and schizophrenia (Takahashi *et al.*, 2010; Takahashi *et al.*, 2013). However, we recognise that this is a small study, and it may be power that limits our capacity to detect true change across both structures. Additionally, for these small structures, high field strength imaging may be required.

The present study supports the role of AI as a marker of early neurodevelopmental change in individuals who are diagnosed with NPC in adulthood. This fits with suggestions that even adult-onset patients have subtle neurodevelopmental changes that occur early in life, present with subtle developmental signs during childhood (such as learning difficulties or subtle clumsiness (Sévin *et al.*, 2007; Walterfang *et al.*, 2006b)), which may persist due to their non-specificity and thus be overlooked until more obvious motor, psychiatric or cognitive changes occur in adulthood.

Longitudinal studies in larger cohorts, perhaps with pooled scans, that examine patients of different illness severity over time and correlate illness indices with these putative brain markers of altered neurodevelopment and/or neuroprogression are warranted.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/neu.2023.43>

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Competing interests. Mark Walterfang has served on advisory boards and received honoraria for consulting from Actelion Pharmaceuticals, Vtesse Pharmaceuticals and Mallinckrodt Pharmaceuticals, who manufacture therapeutic compounds for Niemann-Pick type C.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and “the authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides on the care and use of laboratory animals.”

References

- Arenas F, Garcia-Ruiz C and Fernandez-Checa JC (2017) Intracellular cholesterol trafficking and impact in neurodegeneration. *Frontiers in Molecular Neuroscience* 10, 382.
- Bowman EA, Walterfang M, Abel L, Desmond P, Fahey M and Velakoulis D (2015) Longitudinal changes in cerebellar and subcortical volumes in adult-onset Niemann-Pick disease type C patients treated with miglustat. *Journal of Neurology* 262(9), 2106–2114.
- Carpenter M and Sutin J (1983) Human Neuroanatomy. Baltimore: Williams & Wilkins.
- Carstee ED, Morris JA, Coleman KG, Loftus SK, Zhang D, Cummings C, Gu J, Rosenfeld MA, Pavan WJ, Krizman DB, Nagle J, Polymeropoulos MH, Sturley SL, Ioannou YA, Higgins ME, Comly M, Cooney A, Brown A, Kaneski CR, Blanchette-Mackie EJ, Dwyer NK, Neufeld EB, Chang TY, Liscum L, Strauss JF3rd, Ohno K, Zeigler M, Carmi R, Sokol J, Markie D, O'Neill RR, van Diggelen O P, Elleder M, Patterson MC, Brady RO, Vanier MT, Pentchev PG and Tagle DA (1997) Niemann-Pick C1 disease gene: homology to mediators of cholesterol homeostasis. *Science* 277(5323), 228–231.
- di Biase MA, Zalesky A, O'Keefe G, Laskaris L, Baune BT, Weickert CS, Olver J, McGorry PD, Amminger GP, Nelson B, Scott AM, Hickie I, Banati R, Turkheimer F, Yaqub M, Everall IP, Pantelis C and Cropley V (2017) PET imaging of putative microglial activation in individuals at ultra-high risk for psychosis, recently diagnosed and chronically ill with schizophrenia. *Translational Psychiatry* 7(8), e1225.
- Dremmen MHG, Bouhuis RH, Blanken LME, Muetzel RL, Vernooij MW, Marroun HE, Jaddoe VWV, Verhulst FC, Tiemeier H and White T (2019) Cavum septum pellucidum in the general pediatric population and its relation to surrounding brain structure volumes, cognitive function, and emotional or behavioral problems. *AJNR. American Journal of Neuroradiology* 40(2), 340–346.
- First MB and Gibbon M (2004) The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II). In Comprehensive Handbook of Psychological Assessment. Hoboken, NJ: John Wiley & Sons Inc.
- German DC, Quintero EM, Liang C-L, Ng B, Punia S, Xie C and Dietsch JM (2001) Selective neurodegeneration, without neurofibrillary tangles, in a

- mouse model of Niemann-Pick C disease. *Journal of Comparative Neurology* 433, 415–425.
- Graff-Radford NR (1997) Syndromes due to acquired thalamic damage. In Feinberg TE and Farah MJ (eds), *Behavioural Neurology and Neuropsychology*. New York: McGraw-Hill.
- Iturriaga C, Pineda M, Fernandez-Valero EM, Vanier MT and Coll MJ (2006) Niemann-Pick C disease in Spain: clinical spectrum and development of a disability scale. *Journal of the Neurological Sciences* 249(1), 1–6.
- Landin-Romero R, Amann BL, Sarro S, Guerrero-Pedraza A, Vicens V, Rodriguez-Cano E, Vieta E, Salvador R, Pomarol-Clotet E and Radua J (2016) Midline brain abnormalities across psychotic and mood disorders. *Schizophrenia Bulletin* 42(1), 229–238.
- Lau WM, Lee WR, Miyamoto R, Jung SE, Yanjanin Farhat N, Yoshida S, Mori S, Gropman A, Baker HE and Porter DF (2016) Role of diffusion tensor imaging in prognostication and treatment monitoring in Niemann-Pick disease type C1. *Diseases* 4, 29.
- Lee R, Apkarian K, Jung ES, Yanjanin N, Yoshida S, Mori S, Park J, Gropman A, Baker EH and Porter FD (2014) Corpus callosum diffusion tensor imaging and volume measures are associated with disease severity in pediatric Niemann-Pick disease type C1. *Pediatric Neurology* 51(5), 669–674.e5.
- Love S, Bridges LR and Case CP (1995) Neurofibrillary tangles in Niemann-Pick disease type C. *Brain* 118, 119–129.
- Masingue M, Adanyeguh I, Nadjar Y, Sedel F, Galanaud D and Mochel F (2017) Evolution of structural neuroimaging biomarkers in a series of adult patients with Niemann-Pick type C under treatment. *Orphanet Journal of Rare Diseases* 12, 22.
- Pressey SNR, Smith DA, Wong AMS, Platt FM and Cooper JD (2012) Early glial activation, synaptic changes and axonal pathology in the thalamocortical system of Niemann-Pick type C1 mice. *Neurobiology of Disease* 45(3), 1086–1100.
- Rakic P and Yakovlev PI (1968) Development of the corpus callosum and cavum septi in man. *Journal of Comparative Neurology* 132(1), 45–72.
- Rego T, Farrand S, Goh AMY, Eratne D, Kelso W, Mangelsdorf S, Velakoulis D and Walterfang M (2019) Psychiatric and cognitive symptoms associated with Niemann-Pick type C disease: neurobiology and management. *CNS Drugs* 33(2), 125–142.
- Rosales RK, Lemay MJ and Yakovlev PI (1968) The development and involution of massa intermedia with regard to age and sex. *Journal of Neuropathology and Experimental Neurology* 27(1), 166.
- Samra KA and Cooper IS (1968) Radiology of the massa intermedia. *Radiology* 91(6), 1124–1128.
- Sarwar M (1989) The septum pellucidum: normal and abnormal. *AJNR. American Journal of Neuroradiology* 10(5), 989–1005.
- Sévin M, Lesca G, Baumann N, Millat G, Lyon-Caen O, Vanier MT and Sedel F (2007) The adult form of Niemann-Pick disease type C. *Brain* 130(1), 120–133.
- Shen O, Gelot AB, Moutard ML, Jouannic JM, Sela HY and Garel C (2015) Abnormal shape of the cavum septi pellucidi: an indirect sign of partial agenesis of the corpus callosum. *Ultrasound in Obstetrics & Gynecology* 46(5), 595–599.
- Shunk H (1963) Congenital dilatations of the septi pellucidum. *Radiology* 81(4), 610–618.
- Suzuki K, Parker CC, Pentchev PG, Katz D, Ghatti B, D'Agostino AN and Carstea ED (1995) Neurofibrillary tangles in Niemann-Pick disease type C. *Acta Neuropathologica* 89(3), 227–238.
- Takahashi T, Malhi GS, Wood SJ, Yucel M, Walterfang M, Nakamura K, Suzuki M and Pantelis C (2010) Midline brain abnormalities in established bipolar affective disorder. *Journal of Affective Disorders* 122(3), 301–305.
- Takahashi T, Nakamura K, Ikeda E, Furuichi A, Kido M, Nakamura Y, Kawasaki Y, Noguchi K, Seto H and Suzuki M (2013) Longitudinal MRI study of the midline brain regions in first-episode schizophrenia. *Psychiatry Research: Neuroimaging* 212(2), 150–153.
- Takahashi T, Suzuki M, Hagino H, Niu L, Zhou SY, Nakamura K, Tanino R, Kawasaki Y, Seto H and Kurachi M (2007) Prevalence of large cavum septi pellucidi and its relation to the medial temporal lobe structures in schizophrenia spectrum. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 31(6), 1235–1241.
- Takahashi T, Suzuki M, Nakamura K, Tanino R, Zhou SY, Hagino H, Niu L, Kawasaki Y, Seto H and Kurachi M (2008a) Association between absence of the adhesio interthalamica and amygdala volume in schizophrenia. *Psychiatry Research: Neuroimaging* 162(2), 101–111.
- Takahashi T, Suzuki M, Tsunoda M, Kawamura Y, Takahashi N, Maeno N, Kawasaki Y, Zhou SY, Hagino H, Niu L, Tsuneki H, Kobayashi S, Sasaoka T, Seto H, Kurachi M and Ozaki N (2008b) The association of genotypic combination of the DRD3 and BDNF polymorphisms on the adhesio interthalamica and medial temporal lobe structures. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 32(5), 1236–1242.
- Takahashi T, Suzuki M, Zhou SY, Nakamura K, Tanino R, Kawasaki Y, Seal ML, Seto H and Kurachi M (2008c) Prevalence and length of the adhesio interthalamica in schizophrenia spectrum disorders. *Psychiatry Research: Neuroimaging* 164(1), 90–94.
- Takahashi T, Yucel M, Lorenzetti V, Nakamura K, Whittle S, Walterfang M, Suzuki M, Pantelis C and Allen NB (2009) Midline brain structures in patients with current and remitted major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 33(6), 1058–1063.
- Takahashi T, Yucel M, Yung AR, Wood SJ, Phillips LJ, Berger GE, Ang A, Soulsby B, McGorry PD, Suzuki M, Velakoulis D and Pantelis C (2008d) Adhesio interthalamica in individuals at high-risk for developing psychosis and patients with psychotic disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 32(7), 1708–1714.
- Takahashi T, Yung AR, Yucel M, Wood SJ, Phillips LJ, Harding IH, Soulsby B, McGorry PD, Suzuki M, Velakoulis D and Pantelis C (2008e) Prevalence of large cavum septi pellucidi in ultra high-risk individuals and patients with psychotic disorders. *Schizophrenia Research* 105(1–3), 236–244.
- Trouard TP, Heidenreich RA, Seeger JF and Erickson RP (2005) Diffusion tensor imaging in Niemann-Pick Type C disease. *Pediatric Neurology* 33(5), 325–330.
- Trzesniak C, Kempton MJ, Busatto GF, De Oliveira IR, Galvao-De Almeida A, Kambeitz J, Ferrari MC, Filho AS, Chagas MH, Zuardi AW, Hallak JE, Mcguire PK and Crippa JA (2011a) Adhesio interthalamica alterations in schizophrenia spectrum disorders: a systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 35(4), 877–886.
- Trzesniak C, Oliveira IR, Kempton MJ, Galvao-De Almeida A, Chagas MH, Ferrari MC, Filho AS, Zuardi AW, Prado DA, Busatto GF, Mcguire PK, Hallak JE and Crippa JA (2011b) Are cavum septum pellucidum abnormalities more common in schizophrenia spectrum disorders? A systematic review and meta-analysis. *Schizophrenia Research* 125(1), 1–12.
- Trzesniak C, Schaufelberger MS, Duran FL, Santos LC, Rosa PG, Mcguire PK, Murray RM, Sczufca M, Menezes PR, Hallak JE, Crippa JA and Busatto GF (2012) Longitudinal follow-up of cavum septum pellucidum and adhesio interthalamica alterations in first-episode psychosis: a population-based MRI study. *Psychological Medicine* 42(12), 2523–2534.
- Vanier MT (2010) Niemann-Pick disease type C. *Orphanet Journal of Rare Diseases* 5(1), 16–16.
- Vanier MT (2015) Complex lipid trafficking in Niemann-Pick disease type C. *Journal of Inherited Metabolic Disease* 38(1), 187–199.
- Walkley SU, Baker HJ, Rattazzi MC, Haskins ME and Wu J-Y (1991) Neuroaxonal dystrophy in neuronal storage disorders: evidence for major GABAergic neuron involvement. *Journal of the Neurological Sciences* 104(1), 1–8.
- Walkley SU and Suzuki K (2004) Consequences of NPC1 and NPC2 loss of function in mammalian neurons. *Biochimica et Biophysica Acta* 1685(1–3), 48–62.
- Walterfang M, Fahey M, Abel L, Fietz M, Wood A, Bowman E, Reutens D and Velakoulis D (2011) Size and shape of the corpus callosum in adult Niemann-Pick type C reflects state and trait illness variables. *American Journal of Neuroradiology* 32(7), 1340–1346.
- Walterfang M, Fahey M, Desmond P, Wood A, Seal ML, Steward C, Adamson C, Kokkinos C, Fietz M and Velakoulis D (2010) White and gray matter alterations in adults with Niemann-Pick disease type C. *Neurology* 75(1), LP–56.
- Walterfang M, Fietz M, Fahey M, Sullivan D, Leane P, Lubman DI and DM Velakoulis (2006a) The neuropsychiatry of Niemann-Pick type C disease in adulthood. *The Journal of Neuropsychiatry and Clinical Neurosciences* 18(2), 158–170.

- Walterfang M, Fietz M, Fahey M, Sullivan D, Leane P, Lubman DI and Velakoulis D (2006b) The neuropsychiatry of Niemann-Pick type C disease in adulthood. *The Journal of Neuropsychiatry and Clinical Neurosciences* **18**(2), 158–170.
- Walterfang M, Macfarlane MD, Looi JCL, Abel L, Bowman E, Fahey MC, Desmond P and Velakoulis D (2012) Pontine-to-midbrain ratio indexes ocular-motor function and illness stage in adult Niemann-Pick disease type C. *European Journal of Neurology* **19**(3), 462–467.
- Walterfang M, Patenaude B, Abel LA, Klunenmann H, Bowman EA, Fahey MC, Desmond P, Kelso W and Velakoulis D (2013) Subcortical volumetric reductions in adult Niemann-Pick disease type C: a cross-sectional study. *American Journal of Neuroradiology* **34**(7), 1334–1340.
- Wassif CA, Cross JL, Iben J, Sanchez-Pulido L, Cougnoux A, Platt FM, Ory DS, Ponting CP, Bailey-Wilson JE, Biesecker LG and Porter FD (2016) High incidence of unrecognized visceral/neurological late-onset Niemann-Pick disease, type C1, predicted by analysis of massively parallel sequencing data sets. *Genetics in Medicine* **18**(1), 41–48.
- Wright P, Takei N, Rifkin L and Murray RM (1995) Maternal influenza, obstetric complications, and schizophrenia. *The American Journal of Psychiatry* **152**(12), 1714–1720.
- Zervas M, Dobrenis K and Walkley SU (2001) Neurons in Niemann-Pick disease type C accumulate gangliosides as well as unesterified cholesterol and undergo dendritic and axonal alterations. *Journal of Neuropathology & Experimental Neurology* **60**(1), 49–64.