Journal of the International Neuropsychological Society (2010), **16**, 716–720.

doi:10.1017/S1355617710000500

BRIEF COMMUNICATION

The corpus callosum and empathy in adults with a history of preterm birth

E.J. LAWRENCE, G.M. ALLEN, M. WALSHE, M. ALLIN, R. MURRAY, L. RIFKIN, P.K. MCGUIRE, AND C. NOSARTI

Department of Psychosis Studies, Institute of Psychiatry, King's College London, United Kingdom

(RECEIVED January 18, 2010; FINAL REVISION April 6, 2010; ACCEPTED April 6, 2010)

Abstract

Reduced posterior corpus callosum (CC) area has been consistently observed in children and adolescents born very preterm (VPT). CC structural differences are also observed in people diagnosed with empathy disorders. This study examined empathy in relation to CC size in VPT adults and controls. CC area was manually measured for 17 VPT adults and 9 controls. Participants completed the Interpersonal Reactivity Index (Davis, 1980) and the Empathy Quotient (Baron-Cohen & Wheelwright, 2004). VPT adults had reduced posterior CC area in contrast to controls, and a positive linear trend was observed between posterior CC size and gestational age. No between-group empathy differences were observed, although self-reported personal distress in response to social situations was higher in VPT adults, and negatively associated with anterior CC area. We conclude that VPT adults have a smaller posterior CC, which is associated with gestational age, and elevated social distress, which may be mediated by anterior CC size. (*JINS*, 2010, *16*, 716–720.)

Keywords: White matter, Emotional reactivity, Perspective-taking, Personal distress, Neurodevelopmental, Premature

INTRODUCTION

White matter abnormalities have been observed in children and adolescents born very preterm (VPT: Nosarti et al., 2008). The corpus callosum (CC) is the largest white matter structure in the brain, connecting the hemispheres and underpinning inter-hemispheric processing. Reductions in mid-posterior and posterior CC size have been described in VPT children and adolescents, that is, <33 weeks gestation (Nosarti et al., 2004; Nosarti et al., 2008). These differences may be associated with gestational age, for instance, posterior CC size is reduced in VPT adolescents born at 28–30 weeks, with those born at 31–33 weeks spared (Narberhaus et al., 2007).

Studies that follow VPT individuals into adulthood are limited, and it is not clear whether differences in CC size persist, or represent developmental delay. For instance, a 3.3% CC area increase was observed in healthy controls between 15 and 19 years *versus* 13.4% in VPT participants (Allin et al., 2007). Nevertheless, white matter abnormalities have been observed in the genu of CC in VPT adults (Kontis et al., 2009), and functional and structural differences persist in other brain regions in VPT adults (Lawrence et al., 2009, 2010; Narberhaus et al., 2009; Nosarti et al., 2008).

Empathy is a multi-dimensional construct with cognitive and affective components. Cognitive empathy is to understand what another individual is thinking/feeling, and affective empathy is an emotional response to the mental state of another, excluding self-orientated emotions such as personal distress (Baron-Cohen & Wheelwright, 2004; Davis, 1980). Empathy deficits have been observed in individuals with agenesis of the corpus callosum (Paul et al., 2007), and aberrations in corpus callosum morphology have been found in cohorts with known empathy disturbances such as autistic spectrum disorders (ASDs; Chung et al., 2004). For example, Chung et al. (2004) found reductions in anterior regions (genu and rostrum) alongside reduced white matter density in posterior CC regions in participants diagnosed with ASDs. Whether the decreases in posterior CC area are associated with an empathy deficit in VPT populations has yet to be examined, although increased shyness and low extroversion

Correspondence and reprint requests to: Emma J. Lawrence, Psychosis Studies & Neuroimaging Sciences, PO Box 68, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF UK. E-mail: emma.lawrence@kcl.ac.uk

have been observed in VPT and low birth weight adults (Allin et al., 2006; Schmidt et al., 2008).

The aim of this study was to investigate empathy and CC size in VPT adults and controls using standardized self-report measures and high-resolution structural magnetic resonance imaging (MRI). We administered two empathy questionnaires: the Interpersonal Reactivity Index [IRI] (Davis, 1980) and the Empathy Quotient [EQ] (Baron-Cohen & Wheelwright, 2004). We predicted reduced posterior CC size in VPT adults in comparison to controls, and tested whether such differences were associated with deficits in self-reported empathy.

METHOD

Participants

In 1983–1984, 252 infants born at <33 weeks gestation were admitted within 5 days of birth to the Neonatal Unit at University College London Hospital, survived, and were discharged. All individuals born at <=28 weeks gestation were enrolled for long-term follow-up, as well as a random sample of those born from 29 to 33 weeks gestation. One hundred forty-seven (40% of sample) adolescents were selected for study (78 born at <28 weeks and 69 born at 29–33 weeks gestation). One hundred thirteen individuals were assessed in adolescence; 57 were born at <=28 weeks and 56 from 29 to 33 weeks gestation. In 2003, participants who met the inclusion criteria, i.e., no history of cerebral palsy, grade 3/4 intraventricular hemorrhage, or cystic periventricular leucomalacia, were contacted. Those who responded took part in a series of studies (Lawrence et al., 2009, 2010; Narberhaus et al., 2009). Control participants were also recruited *via* advertisements in the local press and universities. Inclusion criteria were full-term birth (37–42 weeks gestation) and English as a first language; exclusion criteria included birth complications (e.g., birth weight <2500 g, endotracheal mechanical ventilation), prolonged gestation (>42 weeks), history of psychiatric illness, severe hearing and motor impairment.

Twenty-six participants took part in the current study. Ethical approval was obtained from the local committee, and written informed consent was obtained. There were 9 controls (5 male; mean age of 18.9 years ± 1.1) and 17 VPT[1] participants (9 male: mean age of 19.9 ± .8). Mean gestational age for the VPT group was 28.4 (± 2.1) weeks, and mean birth weight was 1212.9 grams (± 3020), and neither statistically differed from the larger cohort from whom they were drawn (gestational age: $t = .78$; $p > .05$; birth weight: $t = .5$; $p > .05$). A total of 35.3% of the sample had an Apgar score between 0 and 3 at 1 min, 35.3% were rated between 4 and 6, and 29.4% scored between 7–10 which is within normal range. These scores did not differ from the distribution in the larger cohort ($X_{(2)} = .1.2$; $p > .05$). There was no difference between the cohorts in the proportion of multiple births ($X_{(5)} = 3.5$; $p > .05$).

Measures

The IRI (Davis, 1980) and EQ (Baron-Cohen & Wheelwright, 2004) were used to assess empathic ability. These gold standard measures tap slightly different aspects of empathy. The EQ contains 40 empathy items, with ratings on a 4-point scale, ranging from, strongly agree to strongly disagree. A score of 0 is allocated for a nonempathic response and 1–2 for an empathic response. The scale was designed to be unifactorial; however, principal components analysis found 13 items correspond to cognitive empathy, including statements such as "I can tell if someone is masking their true emotion with a maximum score of 26"; 9 relate to emotional reactivity such as "seeing people cry doesn't really upset me" with a maximum score of 18; 6 questions relating to social skills, that is, "I often find it difficult to judge whether something is rude or polite" with a maximum score of 12 (Lawrence et al., 2004). The current study results were analyzed using this 28-item solution.

The IRI contains three empathy subscales each with seven items rated on a 5-point scale ranging from "does not describe me at all" to "describes me very well," with, a maximum score of 35. The subscales measure perspective taking, e.g., "I sometimes find it difficult to see things from the other guy's point of view"; empathic concern, e.g., "I often have tender, concerned feelings for people less fortunate than me"; and personal distress, nonempathic self-orientated emotional contagion, e.g., '"Being in a tense emotional situation scares me.".

Procedure

A 1.5 Tesla (T) GE Signa Horizon MRI scanner was used to obtain sagittal T2-weighted fast spin-echo, 27 × 4 mm contiguous slices; axial T2-weighted double-echo fast spin-echo, 28 × 5 mm contiguous slices and three-dimensional T1-weighted gradient-echo sequence that allowed reconstruction in any plane of one hundred twenty-four 1.5-mm slices. CC area was measured on a mid-sagittal slice by subdividing it into four regions by drawing lines perpendicular to its anterior–posterior length using image analysis software Analyze (Nosarti et al., 2004). Inter-rater reliability was performed on five randomly selected CC area measurements from three independent raters (anterior $\alpha = .98$; $p < .001$; mid-anterior $\alpha = .99$; $p < .001$; mid posterior $\alpha = .99$; $p < .001$; posterior $\alpha = .99$; $p < .001$). Total white matter volume was extracted using Voxel-based Morphometry in SPM2.

RESULTS

There were six instances of missing data which were replaced with the mean of the sample, except for data from one

[1] The VPT participant data reported here are a subsample of data reported in Allin et al. (2007). However, the structural data were collected separately, at different time points, and contrasted with a different control group recruited as part of another study (Lawrence et al., 2009, 2010; Narberhaus et al., 2009; Nosarti et al., 2009).

https://doi.org/10.1017/S1355617710000500 Published online by Cambridge University Press

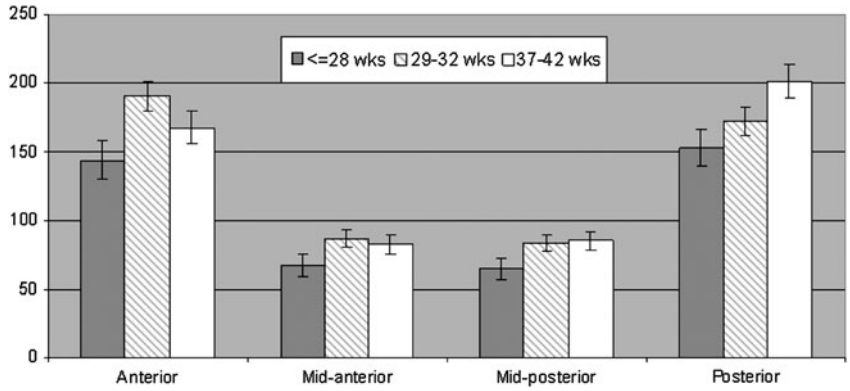

Fig. 1. Mean Corpus Callosum Area in mm^2 by Gestational Age and Adjusted for Age and White Matter Volume. Error bars represent SE of Mean.

control participant who failed to complete six personal distress subscale items and so was excluded from this analysis.

Gender did not differ between groups (X^2 = .016; *df* 1; $p > .05$); however, VPT and control participants did differ in age ($t_{(24)} = 2.8$; $p = .01$), likely due to the narrow age range in the VPT group. Mean Full-Scale IQ estimated by the Wechsler Abbreviated Scale of Intelligence[2] was 106 (± 12) for controls (n = 7) and 98.9 (± 10.4) for VPT participants, with no between-group difference ($t_{(22)} = 1.5$; $p > .05$).

There was no significant between-group difference in total white matter volume ($t_{(24)} = 1.1$; $p > .05$). However, total white matter volume was positively associated with total CC area across groups (r = .53; $p = .003$), so the data were analyzed adjusting for total white matter volume and age. There were no significant differences between controls and VPT adults in total CC area ($F_{(1,22)} = .63$; $p > .05$), anterior CC area ($F_{(1,22)} = .3$; $p > .05$), mid-anterior CC area ($F_{(1,22)} = .03$; $p > .05$), nor mid-posterior CC area ($F_{(1,22)} = .51$; $p > .05$). However, posterior CC area was reduced in VPT adults ($F_{(1,22)} = 4.9$; $p = .04$). In addition, white matter volume more closely related to posterior CC area in controls, than VPT adults ($F_{(1,22)} = 4.6$; $p = .04$).

To examine the influence of gestational age on CC area, the sample was divided into three groups (Lawrence et al., 2010); 1) =< 28 weeks gestation (n = 7), 29–32 weeks gestation (n = 10), 3) controls => 37 weeks gestation (n = 9) – see Figure 1. A significant difference was also observed in anterior CC area between the two VPT groups ($F_{(2,21)} = 3.8$; $p = .04$). No between-group differences were observed in the mid-anterior region ($F_{(2,21)} = 2$; $p > .05$). A near significant positive linear trend was observed for mid-posterior CC area with those with the lowest gestational age having the largest reduction ($F_{(2,21)} = 2.7$; $p = .09$). A positive linear trend was also observed across groups for posterior CC area ($F_{(2,21)} = 4.5$; $p = .02$). Again, white matter volume was more closely related to posterior CC area in controls than VPT participants ($F_{(2,21)} = 5.4$; $p = .03$).

[2] Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence.* New York: The Psychological Corporation.

Empathy

To investigate between-group empathy differences, univariate analyses of variance (ANOVAs) were conducted controlling for age. VPT adults had higher scores on the personal distress subscale of the IRI ($F_{(1,22)} = 4.6$; $p = .04$). No other significant group differences were observed (Table 1). No linear trends in self-reported empathy were observed when dividing participants by gestational age including for personal distress ($F_{(2,21)} = 2.19$; $p = .12$). Kendall's partial correlation analysis adjusted for age revealed a statistical trend indicative of a negative association between personal distress and anterior CC size in VPT ($r = -.38$; p = .07), but not control participants ($r = -.05$; $p = .46$).

DISCUSSION

With total white matter volume adjusted, VPT adults show reduced posterior CC area in contrast to controls. A positive linear trend between posterior CC area and gestational age was also observed, with similar findings for mid-posterior CC area. Participants who were born at <= 28 weeks gestation also had reduced anterior CC size in contrast to VPT adults born nearer term. No significant differences were observed between VPT adults and controls in self-reported empathy, although the VPT group reported increased personal distress in response to social stimuli, in contrast to controls. Correlational analyses suggest this effect may be related to reductions in anterior CC area.

That VPT participants had reduced posterior CC area provides further evidence that structural CC differences observed in younger cohorts persist into adulthood (Caldu et al., 2006; Narberhaus et al., 2007, 2008; Nosarti et al., 2004). We also observed a positive linear trend between gestational age and posterior CC area, and mid-posterior CC area ($p = .09$), suggesting that reductions in CC area may be more severe in those with younger gestational age. CC injury may be partly explained by the vulnerability of the developing corpus callosum to hypoxic–ischemic damage and hemorrhage, possibly due to the intrinsic vulnerability of

https://doi.org/10.1017/S1355617710000500 Published online by Cambridge University Press

Table 1. *Mean* and *SD* Scores on EQ and IRI Subscales Stratified by Group

	Control		Preterm		95% Confidence interval of difference	
	Mean	S.D	Mean	S.D	Lower	Upper
EQ: Cognitive Empathy	15.60	5.38	13.06	6.49	−2.69	7.77
EQ: Emotional Reactivity	10.11	3.62	9.18	3.91	−2.31	4.18
EQ: Social Skills	6.46	3.27	7.65	2.74	−3.67	1.30
EQ: Total	43.97	11.49	41.23	13.06	−7.95	13.42
IRI: Empathic Concern	20.09	3.95	19.46	4.91	−3.29	4.55
IRI: Personal Distress	11.25	5.33	13.88	4.08	−6.62	1.36
IRI: Perspective Taking	17.33	4.58	16.29	6.25	−3.85	5.93

Note. EQ = Empathy Quotient; IRI = Interpersonal Reactivity Index.

immature oligodendrocytes. Previous studies have observed an association between CC size and gestational age in VPT adolescents (Caldu et al., 2006) and the splenium, which encompasses the posterior section of the CC, is only reduced in VPT adolescents with gestational age <= 30 weeks (Narberhaus et al., 2007).

We also observed reductions in anterior CC area in VPT participants of <28 weeks gestation in contrast to those of 29–32 weeks gestation. This is consistent with VPT adolescent data which suggests those with gestational age <27 weeks, to have significantly reduced anterior CC area in contrast to controls (Narberhaus et al., 2007). Although in the current study, participants of 29–32 weeks gestation appeared to have slightly larger anterior CC size than controls, this difference was not statistically significant.

VPT adults did not self-report empathy deficits, and scores for all groups were consistent with normative data for these questionnaires (Lawrence et al., 2004; Lawrence et al, 2006). This suggests differences in CC area may be unrelated or at least not crucial to empathic processing. Previous studies suggest that, although agenesis of the CC leads to high psychiatric morbidity, this is unrelated to any specific pathology (Taylor & David, 1998). However, it is also possible that this finding is due to the processes of cognitive or neural plasticity, for instance, VPT adults have been previously found to recruit additional brain structures for successful task completion (Lawrence et al., 2009, 2010).

VPT adults did, however, report higher rates of personal distress than controls. Personal distress is an emotional reaction to social situations, which is self-orientated. Although not an empathic response, it is a form of emotional contagion which includes feelings of unease and distress (Lawrence et al., 2006). These data are consistent with other personality differences in VPT adults such as elevated anxiety (Allin et al., 2006), increased shyness, and reduced extroversion (Schmidt et al., 2008).

A statistical trend indicated that differences in anterior CC size may be modestly associated with personal distress in VPT adults, with larger anterior CC reductions associated with increased personal distress. Previous studies have found structural differences in the anterior CC, which contains interhemispheric fibers connecting different sections of the prefrontal cortex, to be associated with prefrontal functions in VPT adolescents (Narberhaus et al., 2008). It has been suggested that personal distress may result from a lack of downregulation of a vicarious affective response (Lawrence et al., 2006), a skill requiring prefrontal inhibition mechanisms. Consistently, the anterior CC is larger in participants with an enhanced ability to downregulate pain (Horton et al., 2004). This account may explain the association observed between personal distress and anterior CC size in VPT adults. Future studies are needed to determine whether differences in emotion regulation in VPT adults of low gestational age underpin observed personality differences (Allin et al., 2006; Schmidt et al., 2008).

Overall, these data are limited by being reliant on self-report. The small sample size and lack of statistical power may also have prevented the observation of between-group empathy differences, as response rate for controls for was lower than for the VPT group. However, this is unlikely as the reported empathy scores were consistent with normative data. As hypothesized, VPT adults had significantly smaller posterior CC area than controls, which was related to gestational age. In addition, VPT participants with a gestational age <=28 weeks had reduced anterior CC size, in contrast to VPT adults born nearer term, and this may be related to their increased levels of personal distress. Further studies with a larger sample size are warranted, and it would be prudent to use recent advances in neuroimaging methods such as Diffusion Tensor Imaging and connectivity analyses.

ACKNOWLEDGMENTS

We thank all the participants for giving their time and Anastasia Kalpakidou for her help with data collection. We can confirm that there are no potential or real conflicts of interest. This work was supported by grants awarded by the March of Dimes Birth Defects Foundation, USA (12-FY03-4); and the Health Foundation, UK (1206/2063) to RMM, CN, PKM and LR.

REFERENCES

Allin, M., Nosarti, C., Narberhaus, A., Walshe, M., Frearson, S., Kalpakidou, A., et al. (2007). Growth of the corpus callosum in adolescents born preterm. *Archives of Pediatric Adolescent Medicine*, *161*, 1183–1189.

Allin, M., Rooney, M., Cuddy, M., Wyatt, J., Walshe, M., Rifkin, L., et al. (2006). Personality in young adults who were born preterm. *Pediatrics*, *117*, 309–316.

Baron-Cohen, S., & Wheelwright, S. (2004). The empathy quotient: An investigation of adults with Asperger's syndrome or high functioning autism, and normal sex differences. *Journal of Autism & Developmental Disorders*, *34*, 163–175.

Caldu, X., Narberhaus, A., Junque, C., Gimenez, M., Vendrell, P., Bargallo, N., et al. (2006). Corpus callosum size and neuropsychological impairment in adolescents who were born preterm. *Journal of Child Neurology*, *21*, 406–410.

Chung, M., Dalton, K., Alexander, A., & Davidson, R. (2004). Less white matter concentration in autism: 2D voxel-based morphometry. *Neuroimage*, *23*, 242–251.

Davis, M. (1980). A multidimensional approach to individual differences in empathy. *Catalog of Selected Documents in Psychology*, *10*, 85.

Horton, J., Crawford, H., Harrington, G., & Hunter-Downs, J. (2004). Increased anterior corpus callosum size associated positively with hypnotizability and the ability to control pain. *Brain*, *127*, 1741–1747.

Kontis, D., Canti, M., Cuddy, M., Walshe, M., Nosarti, C., Jones, D., et al. (2009). Diffusion tensor MRI of the corpus callosum and cognitive function in adults born preterm. *Neuroreport*, *20*, 424–428.

Lawrence, E.J., McGuire, P.K., Allin, M., Walshe, M., Giampietro, V., Murray, R.M., et al. (2010). The very preterm brain in young adulthood: The neural correlates of verbal paired associate learning. *Journal of Pediatrics*, [Epub ahead of print].

Lawrence, E.J., Rubia, K., Murray, R., McGuire, P.K., Walshe, M., Allin, M., et al. (2009). The neural basis of response inhibition and attention allocation as mediated by gestational age. *Human Brain Mapping*, *30*, 1038–1050.

Lawrence, E.J., Shaw, P., Baker, D., Baron-Cohen, S., & David, A.S. (2004). Measuring empathy - Reliability and validity of the empathy quotient. *Psychological Medicine*, *34*, 911–919.

Lawrence, E.J., Shaw, P., Giampietro, V.P., Surguladze, S., Brammer, M.J., & David, A.S. (2006). The role of 'shared representations' in social perception and empathy: An fMRI study. *Neuroimage*, *29*, 1173–1184.

Narberhaus, A., Lawrence, E.J., Allin, M., Walshe, M., McGuire, P., Rifkin, L., et al. (2009). Neural substrates of visual paired associates in young adults with a history of very preterm birth: Alterations in fronto-parieto-occipital networks and caudate nucleus. *Neuroimage*, *47*, 1884–1893.

Narberhaus, A., Segarra, D., Caldu, X., Gimenez, M., Junque, C., Pueyo, R., et al. (2007). Gestational age at preterm birth in relation to corpus callosum and general cognitive outcome in adolescents. *Journal of Child Neurology*, *22*, 761–765.

Narberhaus, A., Segarra, D., Caldu, X., Gimenez, M., Pueyo, R., Botet, F., et al. (2008). Corpus callosum and prefrontal functions in adolescents with history of very preterm birth. *Neuropsychologia*, *46*, 111–116.

Nosarti, C., Giouroukou, E., Healy, E., Rifkin, L., Walshe, M., Reichenberg, A., et al. (2008). Grey and white matter distribution in very preterm adolescents mediates neurodevelopmental outcome. *Brain*, *131*, 205–217.

Nosarti, C., Rushe, T.M., Woodruff, P.W., Stewart, A.L., Rifkin, L., & Murray, R.M. (2004). Corpus callosum size and very preterm birth: Relationship to neuropsychological outcome. *Brain*, *127*, 2080–2089.

Paul, L.K., Brown, W.S., Adolphs, R., Tyszka, J.M., Richards, L.J., Mukherjee, P., et al. (2007). Agenesis of the corpus callosum: Genetic, developmental and functional aspects of connectivity. *Nature Review Neuroscience*, *8*, 287–299.

Schmidt, L., Miskovic, V., Boyle, M., & Saigal, S. (2008). Shyness and timidity in young adults who were born at extremely low birth weight. *Pediatrics*, *122*, e181–e187.

Taylor, M., & David, A.S. (1998). Agenesis of the corpus callosum: A United Kingdom series of 56 cases. *Journal of Neurology, Neurosurgery, and Psychiatry*, *64*, 131–134.