Psychological Medicine (2010), **40**, 945–954. © Cambridge University Press 2009
doi:10.1017/S0033291709990870 Printed in the United Kingdom

ORIGINAL ARTICLE

Amygdala volume in a population with special educational needs at high risk of schizophrenia

K. A. Welch*, A. C. Stanfield, T. W. Moorhead, K. Haga, D. C. G. Owens, S. M. Lawrie and E. C. Johnstone

Division of Psychiatry, School of Molecular and Clinical Medicine, University of Edinburgh, Edinburgh, UK

Background. The mildly learning disabled population has a three-fold elevated risk for schizophrenia. It has been proposed that in some individuals this cognitive limitation is a pre-psychotic manifestation of early onset schizophrenia. We examined clinical and neuroanatomical measures of a putative extended phenotype of schizophrenia in an adolescent population receiving special educational assistance. We predicted that people with intellectual impairment and schizotypal features would exhibit amygdala volume reduction as one of the neuroanatomical abnormalities associated with schizophrenia.

Method. Assessment by clinical interview, neuropsychological assessment and magnetic resonance imaging scanning was carried out in 28 intellectually impaired individuals identified as being at elevated risk of schizophrenia due to the presence of schizotypal traits, 39 intellectually impaired controls and 29 non-intellectually impaired controls. Amygdala volume was compared in these three groups and the relationship between symptomatology and amygdala volume investigated.

Results. Right amygdala volume was significantly increased in the elevated risk group compared with the intellectually impaired controls ($p=0.05$). A significant negative correlation was seen between left amygdala volume and severity of negative symptoms within this group ($p<0.05$), but not in either control group.

Conclusions. Intellectually impaired subjects judged to be at elevated risk of schizophrenia on the basis of clinical assessment exhibit structural imaging findings which distinguish them from the generality of learning disabled subjects. Within this population reduced amygdala volume may be associated with negative-type symptoms and be part of an extended phenotype that reflects particularly elevated risk and/or early manifestations of the development of psychosis.

Received 16 February 2009; Revised 16 June 2009; Accepted 24 June 2009; First published online 7 September 2009

Key words: Amygdala, cognitive impairment, high risk, learning disability, magnetic resonance imaging, schizophrenia.

Introduction

There is a well-established relationship between schizophrenia and cognitive impairment at all stages of the illness – pre-morbidly (Niemi *et al*. 2003), during the acute phase (Johnstone *et al*. 2002) and in chronic illness (Cunningham Owens & Johnstone, 1980). It is also well recognized that in people with mild 'learning disability' [intelligence quotient (IQ) between 50 and 70, International Classification of Diseases (ICD-10); WHO, 1992], schizophrenia is relatively common, with a prevalence three to five times that of the general population (Turner, 1989; Morgan *et al*. 2008). The association between schizophrenia and cognitive impairment could arise from two main possibilities. First, it may be that restricted cognitive function increases the vulnerability to schizophrenia, the suggested mechanism being the overload on comprehension imparted by partly understood stimuli (Doody *et al*. 1998). Alternatively, the presence of a schizophrenic diathesis may itself form the underlying basis of evident cognitive impairment; this, possibly together with motor and social impairment, being the initial symptom of severe schizophrenia.

In an attempt to clarify these issues, previous studies in our department compared subjects with co-morbid schizophrenia and learning disability with individuals with learning disability alone and schizophrenia alone in terms of clinical, imaging and genetic parameters (Doody *et al*. 1998; Sanderson *et al*. 1999; Bonnici *et al*. 2007). Structural brain changes in the co-morbid sample were reported to strongly resemble

* Address for correspondence: K. A. Welch, Division of Psychiatry, School of Molecular and Clinical Medicine, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh EH10 5HF, UK.
(Email: kwelch1@staffmail.ed.ac.uk)

those of the schizophrenic sample and be very different from the group with learning disability alone. Smaller amygdala–hippocampal complexes (AHC) relative to whole-brain size were seen in both schizophrenic populations, but not the non-schizophrenic learning disabled group. In addition, the co-morbid population had high rates of chromosomal variants and abnormalities (Muir *et al*. 1998; Johnstone *et al*. 2007). These results are consistent with a postulate that this co-morbidity principally represents a form of severe schizophrenia, and opens up the possibility that within the young learning disabled population there may be individuals whose cognitive deficits are part of the natural history of an illness where the clinical features that define schizophrenia have yet to become manifest.

Volume reduction of the AHC and indeed the individually measured amygdala and hippocampus are in fact some of the most replicated structural magnetic resonance imaging (MRI) findings in established schizophrenia (Lawrie & Abukmeil, 1998; Wright *et al*. 2000). There is also evidence that this volume loss may predate psychosis (Lawrie *et al*. 2008).

The current study, arising from the Edinburgh Study of Co-morbidity (ESC), concerns a group of individuals at enhanced risk of schizophrenia for both cognitive and behavioural reasons. They were receiving special educational support for evident cognitive difficulties and also scored highly on the Structured Interview for Schizotypy (SIS) (Kendler *et al*. 1989) and the Childhood Behaviour Checklist (CBCL) (Achenbach, 1991), measures found to predict schizophrenia in the Edinburgh High Risk Study (EHRS). Previous studies on this group have demonstrated that they share neuropsychological and neuroanatomical similarities with those at high risk of schizophrenia for familial reasons. Specifically they exhibit increased right prefrontal gyrification (Stanfield *et al*. 2008*b*) have high rates of partial psychotic symptoms (Johnstone *et al*. 2007), and have impairments on tests of memory and executive function when compared with IQ-matched controls (Johnstone *et al*. 2005, 2007). This suggests that, despite the ESC population being identified in quite a different way from the genetically high-risk EHRS population, in both contexts these scales are identifying a subgroup of individuals particularly likely to develop schizophrenia and sharing common features. Considering this, together with the increasing evidence that disruption of amygdala structure and function may be associated with emotion processing abnormalities and symptoms in schizophrenia (Kapur, 2003; Gur *et al*. 2007), we hypothesized that this group would show reductions in amygdala volume compared with controls and that the degree of volume reduction would correlate with measures of symptom severity.

Method

Recruitment and assessment

Subject recruitment occurred as part of the ESC, the aim of which is to examine the neurobiological features of psychiatric disorders in adolescents with cognitive impairment. Full details of recruitment are available elsewhere (Johnstone *et al*. 2007). Briefly, schools and colleges throughout Scotland were contacted and asked to identify young people receiving special educational assistance. As IQ is not routinely measured in the Scottish educational system, teachers were asked to identify adolescents who were functioning at a level consistent with an estimated IQ of between 50 and 80. This identification was on the basis of the teacher's global impression. Exclusion criteria at recruitment were a known chromosomal abnormality, severe cerebral palsy, profound learning disability, lack of speech and a known brain injury. All potential participants were then screened using the SIS and the CBCL. Cut-offs on these instruments had been found to predict the later development of schizophrenia in the EHRS (Miller *et al*. 2002; Johnstone *et al*. 2005). On the basis of cut-off scores on these two instruments (30.5 for the SIS and 85.5 for the CBCL), four cells were filled comprising individuals with 'high' scores on each, 'low' scores on each, and 'high' on one and 'low' on the other. These cells were then sampled randomly so that the final sample contained 168 participants with approximately equal numbers from each cell. This study concerns the group that scored 'high' on both screens (SIS+/CBCL+ group) and the group that scored 'low' on both (SIS−/CBCL− group), the latter serving as IQ-matched controls (Johnstone *et al*. 2007). None of these participants had a history of psychotic illness, antipsychotic medication or substance use. An additional control group of age-matched young people with no history of psychiatric disorder or special educational requirements was recruited through youth and voluntary organizations in the areas from which the sample came and was subject to the same investigations.

Each participant received a measure of IQ using the Wechsler Intelligence Scale for Children or the Wechsler Adult Intelligence Scale (as appropriate to the individual's age) (Wechsler, 1992, 1999) and a rating of their current symptomatology using the Positive and Negative Syndrome Scale (PANSS; Kay *et al*. 1987). All clinical ratings were done blind to CBCL/SIS cell allocation. Each participant also received a structural MRI scan.

https://doi.org/10.1017/S0033291709990870 Published online by Cambridge University Press

MRI protocol and image processing

MRI was performed at the Scottish Higher Education Funding Council (SHEFC) Brain Imaging Research Centre for Scotland on a 1.5T GE Signa Echospeed system (GE Medical Systems, USA) operating in research mode consisting of a T1-weighted sagittal sequence with parameters of echo time (TE) = 16 ms, repetition time (TR) = 450 ms, excitations = 0.75 and a T2-weighted axial sequence with parameters of TE = 102 ms, TR = 6300 ms, excitations = 2. Volume data were obtained with a three-dimensional inversion-recovery prepared T1-weighted sequence with parameters of TE = 3.3 ms, TR = 8.1 ms, excitations = 1, inversion delay (TI) = 600 ms, flip angle = 15°, slice thickness = 1.7 mm (no gap), matrix = 256 × 192, field of view = 220 mm.

Amygdala measurement

In vivo assessment of amygdala volume by MRI is generally recognized as challenging (Convit *et al*. 1999). The amygdala and structures surrounding it have similar signal intensities, a fact which makes accurate delineation of amygdala boundaries difficult. Perhaps unsurprisingly, therefore, a striking feature of studies that have addressed the measurement of the amygdala both in subjects with and without schizophrenia is the wide range of volumes encountered (Pruessner *et al*. 2000; Wright *et al*. 2000). It is recognized that methodologies that rely heavily on external landmarks tend to yield larger amygdala sizes (Chance *et al*. 2002). The method of amygdala measurement described by Schumann *et al*. (2004) was employed as the basis of our tracing protocol, as this does not rely heavily on external landmarks (Schumann *et al*. 2004). All tracing was undertaken with frequent reference to an atlas of neuroanatomy to further ensure accuracy of anatomical delineation (Duvernoy, 1999). Tracing was primarily undertaken by K.W., with A.S. tracing duplicate scans to determine inter-rater reliability. The tracing protocol demonstrated an inter-rater reliability of 0.80, and an intra-rater reliability of 0.84 on 15 randomly selected amygdalae.

Statistical analysis

All statistical analyses were carried out using SPSS 14.0 for Windows (SPSS Inc., USA). The 28 SIS+/CBCL+ subjects, 39 SIS−/CBCL− subjects and 29 unrelated controls were compared with regard to demographic and clinical characteristics. Between-group differences were tested using χ^2 analyses for categorical variables and analysis of variance (ANOVA) for continuous variables.

Whole-brain volume was compared between the groups using analysis of covariance (ANCOVA) with whole-brain volume as the dependent variable, group and gender as fixed factors and age as a covariate.

Raw amygdala volumes were compared between the groups using ANOVA. Due to significant differences in gender ratio and brain volume between the groups, ANCOVA was then employed with amygdala volume as the dependent variable, group and gender as fixed factors and whole-brain volume and age as covariates. Standardized residual plots were checked for normality and the assumption of homogeneity of regression slopes was met. Within each of the three groups partial correlation coefficients controlling for whole-brain volume, age and gender were used to examine the relationship between amygdala volume and clinical variables as assessed by PANSS.

Results

The demographic characteristics of the three groups under study are detailed in Table 1. There was a significant overall gender imbalance between the groups, and gender was therefore used as a covariate in between-group analyses. After adjustment for age and gender, whole-brain volume was found to differ significantly between the three groups [$F(2, 91) = 3.65$, $p = 0.03$]. *Post-hoc* analysis revealed that though the difference in whole-brain volume between the unrelated control and SIS+/CBCL+ groups was non-significant, that between the unrelated controls and SIS−/CBCL− subjects was clearly significant ($p = 0.009$).

Comparison of amygdala volume in study and control groups

Raw amygdala volumes are detailed in Table 2, together with comparison of the three groups by ANOVA. As can be seen from the pairwise analysis, both right and left amygdalae were larger in the SIS+/CBCL+ group compared with the SIS−/CBCL− group; this difference was significant on the right side ($p = 0.020$), and approached significance on the left ($p = 0.054$). Analysis was repeated by ANCOVA, covarying for age, gender and whole-brain volume; these results are detailed in Table 3. The ANCOVA analysis showed a weak trend towards the main effect [$F(2, 93) = 2.41$, $p = 0.096$] for the right amygdala. Between-group comparisons revealed a significantly larger right amygdala in the SIS+/CBCL+ group *versus* the SIS−/CBCL− group ($p = 0.05$), and a trend towards a larger right amygdala in the SIS+/CBCL+ group compared with normal controls ($p = 0.068$). Although left amygdala volume was also greater in

https://doi.org/10.1017/S0033291709990870 Published online by Cambridge University Press

Table 1. *Demographic characteristics, IQ and mean CBCL and SIS scores for SIS+/CBCL+ subjects, SIS−/CBCL− subjects and unrelated controls*

	SIS+/CBCL+ ($n=28$)	SIS−/CBCL− ($n=39$)	Non-intellectually impaired controls ($n=29$)	p[a]
Age, years	16.09 (1.88)	16.47 (1.48)	16.45 (1.71)	0.57
Gender, *n*				0.02
Male	20	22	10	
Female	8	17	19	
Height, cm	166.85 (9.58)	167.35 (8.71)[b]	167.96 (10.22)	0.91
Full IQ	74.64 (17.95)	73.33 (16.56)	104.65 (18.14)	<0.01
Whole-brain volume, cm^3	1352.75 (176.08)	1301.74 (175.46)	1359.06 (147.11)	0.03
SIS	38.50 (8.04)	21.26 (6.28)	18.52 (6.01)	<0.01
CBCL	111.82 (17.88)	51.77 (22.82)	14.17 (12.02)	<0.01
PANSS symptoms				
Total	47.37 (12.41)	37.29 (5.63)	32.52 (3.30)	<0.01
Positive	10.00 (2.75)	7.90 (1.68)	7.39 (0.84)	<0.01
Negative	12.78 (6.31)	10.23 (3.58)	7.70 (1.72)	<0.01
General	24.59 (6.28)	19.13 (3.31)	17.43 (2.17)	<0.01

Values are given as mean (standard deviation).

IQ, Intelligence quotient; CBCL, Childhood Behaviour Checklist; SIS, Structured Interview for Schizotypy; PANSS, Positive and Negative Syndrome Scale.

[a] Results of ANOVA analysis comparing the three groups, except for the gender comparison for which χ^2 was used, and comparison of whole-brain volumes for which ANCOVA was used with gender and age included as covariates.

[b] Data missing for two subjects.

the SIS+/CBCL+ group than both the SIS−/CBCL− and normal control groups, this finding did not reach significance.

Analyses within the study groups

The results of the partial correlations between amygdala volume and PANSS scores are shown in Table 4. A significant negative correlation was seen between score on the negative subset of symptoms on the PANSS and left amygdala volume [$r=-0.43$, p (two-tailed) 0.039] (Fig. 1), no such relationship being seen in either comparator group. To exclude the possibility that skew or outliers were driving a spurious association, analysis was repeated using a log transformation. This reduced the measure of skewness, and led to an increase in the linear association ($r=-0.40$, $p=0.043$). The partial correlation also remained significant ($r=-0.42$, $p=0.043$).

Discussion

In this study of cognitively impaired individuals we found that, rather than amygdala volume being reduced in the high-risk group compared with either control group, it was in fact increased. We also identified a significant negative association between severity of negative symptoms and volume of the left amygdala within the SIS+/CBCL+ group.

The former finding was not expected at the outset of the study. At first consideration it appears to stand in contrast to results from the EHRS, in which the AHC was found to be reduced in volume in a high-risk population, even prior to the onset of psychosis and that this volume loss was evident throughout the length of the AHC (Lawrie *et al*. 2001, 2003). It is important to stress, however, that though the finding of reduced amygdala volume is one of the most replicated in chronic schizophrenia, data from individuals who are well, though destined to become psychotic, are notably sparse. Another prominent study aiming to identify vulnerability markers predicting schizophrenia before frank psychosis is that conducted in the Personal Assessment and Crisis Evaluation clinic in Melbourne, Australia. In contrast to the Edinburgh group, this study used a 'close in' strategy to identify those symptomatic, clinically compromised, and help-seeking individuals at imminent risk of developing a florid psychosis, but not yet

https://doi.org/10.1017/S0033291709990870 Published online by Cambridge University Press

Table 2. *Raw amygdala volume (cm³) in SIS+/CBCL+, SIS−/CBCL− and control subjects compared by ANOVA*

	Right amygdala					Left amygdala				
			Analysis					Analysis		
				Pairwise					Pairwise	
	Mean	(S.D.)	General	SIS+/CBCLv+ *v.* controls	SIS+/CBCL+ *v.* SIS−/CBCL−	Mean	(S.D.)	General	SIS+/CBCL+ *v.* controls	SIS+/CBCL+ *v.* SIS−/CBCL−
SIS+/CBCL+	1.396	(0.346)	$F=2.96$,	$p=0.083$	$p=0.020$	1.365	(0.312)	$F=2.09$, df=2,	$p=0.121$	$p=0.054$
SIS−/CBCL−	1.243	(0.263)	df=2, 93,			1.247	(0.231)	93, $p=0.013$		
Unrelated controls	1.275	(0.127)	$p=0.057$			1.264	(0.177)			

SIS, Structured Interview for Schizotypy; CBCL, Childhood Behaviour Checklist; ANOVA, analysis of variance; S.D., standard deviation; df, degrees of freedom.

Table 3. *Comparison of amygdala volume in the three groups after covariation for gender, age and whole-brain volume*

							Pairwise comparisons	
	Adjusted amygdalae volumes, cm³ (S.D.)			ANCOVA			SIS+/CBCL+ *v.* controls	SIS+/CBCL+ *v.* SIS−/CBCL−
	SIS+/CBCL+	SIS−/CBCL−	Controls	*F*	df	*p*	*p*	*p*
Right amygdala	1.383 (0.047)	1.264 (0.039)	1.259 (0.046)	2.41	2, 90	0.096	0.068	0.050
Left amygdala	1.358 (0.044)	1.272 (0.037)	1.244 (0.043)	1.84	2, 90	0.164	0.075	0.131

S.D., Standard deviation; ANCOVA, analysis of covariance; SIS, Structured Interview for Schizotypy; CBCL, Childhood Behaviour Checklist; df, degrees of freedom.

Table 4. *Partial correlation between score on the PANSS and amygdala volume within the study group, with covariation for gender, age and whole-brain volume*

		PANSS positive	PANSS negative	PANSS general	PANSS total
Right amygdala	Correlation	0.010	−0.150	0.159	0.018
	p	0.962	0.483	0.459	0.934
Left amygdala	Correlation	0.090	−0.429	0.126	−0.127
	p	0.676	0.037	0.557	0.555

PANSS, Positive and Negative Syndrome Scale.

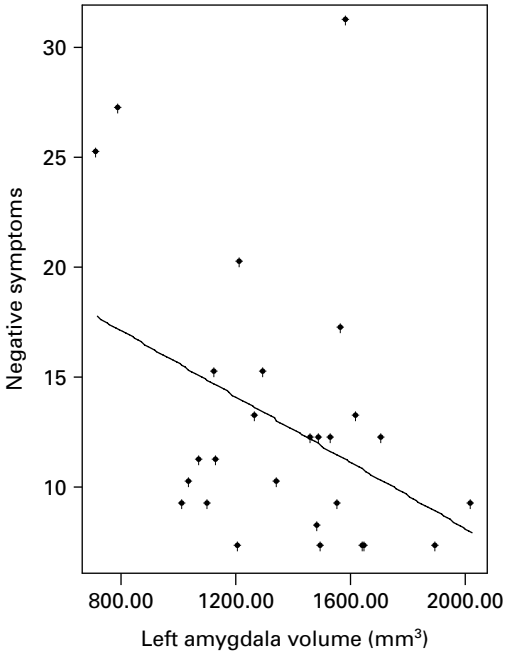

Fig. 1. Left amygdala volume and score on the negative subset of the Positive and Negative Syndrome Scale for the group with high scores on both the Structured Interview for Schizotypy and the Childhood Behaviour Checklist.

actively psychotic; a group labelled 'ultra-high risk' (Velakoulis *et al*. 2006). In one study of this population the amygdala itself was measured using region of interest methodology (Velakoulis *et al*. 2006). This study reported normal amygdala volume in ultra-high-risk subjects, a finding replicated in a subsequent Swiss voxel-based morphometry study of patients with a similarly at-risk mental state (Borgwardt *et al*. 2007). Thus, despite robust data indicating reduced amygdala volume in established schizophrenia, the presence or absence of changes prior to onset of the disorder have not yet been well established.

Other interpretations for the apparent differences between the EHRS results we have reported before and the ESC results reported here need to be considered. One possibility is that these are attributable to the younger age of the ESC population. More intriguing is the possibility that the SIS and CBCL are identifying individuals within the intellectually impaired group with specific, but non-schizophrenifrom, conditions. Autism is one such possibility, and given the evidence that brain volumes are enlarged in autism (Stanfield *et al*. 2008*a*), perhaps particularly in those with autism and low IQ, it is conceivable that the schizotypal population may also have autistic features. This possible overlap between the schizophrenia and autism spectra is being addressed in other studies in which we are currently engaged. It is also possible that the measures are identifying individuals with other conditions, such as affective disorders or personality disorders. However, given the previously reported neuroanatomical and neuropsychological similarities between the group under study and those at risk of schizophrenia for familial reasons this seems unlikely.

It is interesting to note that, although non-significant, there is a higher proportion of males in the SIS+/CBCL+ group compared with the SIS−/CBCL− group. This is in keeping with previous studies identifying an excess of males in those with schizophrenia from a learning disabled population (Cooper *et al*. 2007). Although the difference is non-significant we did include gender as a covariate in our analysis; hence the excess of males is unlikely to account for the results we report.

The finding of significantly larger right amygdala volume in the SIS+/CBCL+ compared with the SIS−/CBCL− group, even after controlling for the larger whole-brain volume of the former, is striking. It suggests that there are structural brain differences associated with the clinical features differentiating these two intellectually impaired groups which we predict to be at relatively high and low risk of schizophrenia. The whole-brain volume of the SIS−/CBCL− intellectually impaired group is significantly smaller than that of the normal control group, but there is no significant difference in whole-brain volume between the SIS+/CBCL+ and normal control group. Those

https://doi.org/10.1017/S0033291709990870 Published online by Cambridge University Press

intellectually impaired individuals posited to be at elevated risk for schizophrenia appear to have different structural brain imaging characteristics (here, preferentially affecting the amygdala) from the generality of learning disabled individuals (who tend to have reduced whole-brain volume). This is of particular interest when considered with the findings of previous studies comparing structural imaging findings in subjects co-morbid for schizophrenia and learning disability with those with schizophrenia and learning disability alone. As noted in the Introduction, these studies reported that structural brain changes in the co-morbid sample were very different from those with learning disability alone, though generally indistinguishable from those in non-learning disabled subjects with schizophrenia (Sanderson *et al*. 1999; Moorhead *et al*. 2004; Bonnici *et al*. 2007). The current findings extend these observations to suggest that intellectually impaired subjects who are not yet psychotic but judged to be at elevated risk of schizophrenia in terms of clinical assessment can be distinguished from the generality of intellectually impaired subjects on the basis of structural imaging findings.

If it is the case that enlarged amygdala volume is a feature of elevated risk for schizophrenia, how can this be reconciled with the reduced amygdala volume seen in established schizophrenia? This would imply that the development of a frank schizophrenic illness involves amygdala volume loss, and that this process may in itself contribute to the development of schizophrenic psychopathology. A possible mechanism that could account for this process is one of amygdala hyperactivity and subsequent atrophy, these changes potentially being triggered by events such as exposure to environmental stressors. Indeed, this explanation has previously been posited to explain amygdala volume loss with time in children with autism (Nacewicz *et al*. 2006). It may be that structurally abnormal amygdalae, such as the abnormally large structures found in the SIS+/CBCL+ subjects, are particularly vulnerable to this process. As they are currently early in the development of illness (and yet to manifest frank psychotic symptoms), little of this atrophy has yet occurred, so explaining their relatively greater volume at the time of assessment.

If the above explanation were true, then we would expect that within the SIS+/CBCL+ group those who were beginning the transition to a schizophrenic illness would exhibit amygdala volume loss. This is indeed what may be suggested by the second finding of this study, the significant negative correlation between left amygdala volume and severity of negative symptoms. It is possible that this is a consequence of some of the SIS+/CBCL+ subjects beginning the process of transition to schizophrenia, this being associated with a loss of amygdala volume which manifests clinically as the development of negative symptoms. That these at-risk individuals are losing amygdala volume over time is given further credence by additional analysis of this dataset. Tensor-based morphometry analysis of subjects scoring above cut-off on the SIS confirms left amygdala volume loss in this at-risk group over an 18-month period following from these baseline scans. This strongly suggests that a dynamic process of amygdala volume loss is indeed occurring in these subjects (Moorhead *et al*. in press).

In the discussion above the co-occurrence of negative symptoms and reduced amygdala volume in the SIS+/CBCL+ group is attributed to both being manifestations of an underlying schizophrenic diathesis. It could be argued, however, that negative symptoms may simply be manifestations of learning disability (for example, representing general functional impairment), and the greater the severity of this the smaller the amygdala. The absence of a similar association between reduced amygdala volume and negative symptoms in the SIS−/CBCL− group makes this explanation improbable, though to fully address this possibility we would ideally ascertain if characteristics such as functional impairment independently correlated with amygdala volume. Unfortunately, no such measures were included in the study, and this could be regarded as a potential weakness. Conversely, however, though data are sparse, schizophrenia associated with learning disability is recognized as exhibiting a particularly pronounced deficit state (Doody *et al*. 1998; Hassiotis *et al*. 1999). This would fit with the possibility that both the psychosis and cognitive impairment of co-morbid populations are manifestations of a 'severe schizophrenia', and suggest that the negative symptoms exhibited by SIS+/CBCL+ individuals in this study are indeed early manifestations of an underlying schizophrenic diathesis.

The association described above is given greater credence if a hypothesis can be described by which amygdala dysfunction results in negative symptoms. Such a model has been suggested by Grossberg. He proposes that the emotional centres of the brain (in particular the amygdala) interact with sensory and prefrontal cortices to generate affective states and elicit motivated behaviours (Grossberg, 2000). If emotional centres become depressed, feedback loops are disturbed and negative symptoms can emerge. A primary lesion in the amygdala can thus have widespread effects, with a reduction in incentive motivating signals from depressed amygdala circuits projecting to the prefrontal cortex being one possible cause of the decreased prefrontal activity seen in schizophrenia.

On considering the model described above, the relevance of findings from this study are potentially significant. From the above it would be expected that if an individual experiences reduced incentive motivating signals to the prefrontal cortex, these would be clinically manifest as negative-type symptoms. These could be present for many years before psychosis is present and, together with cognitive deficits, be clinically manifest as learning disability. Thus, in a population at elevated risk of schizophrenia but not yet psychotic, a greater weight of negative symptoms could reflect greater impairment of incentive motivating signals from an abnormal amygdala. This impairment of amygdala function would be expected to be due to abnormal development of the structure, which may have been present from very early life. Such a structure may be more vulnerable to further insults, which occur during the period of (and may contribute to the transition to) schizophrenia. It seems logical to expect that the greater the extent of the lesion to the amygdala, the greater the impairment of its function. Thus, if the structure experiences further damage, then the weight of negative symptoms increases. Additionally, ongoing damage may well be significant in the development of positive symptoms.

The unilateral nature of this association must be acknowledged, but is in fact compatible with this model. Amygdala volume loss in schizophrenia has been reported as more notable on the left, and when identified unilaterally it is generally on this side (Shenton *et al*. 2001; Honea *et al*. 2005). That amygdala volume loss may occur earlier on the left side is suggested by meta-analysis of first-episode case–control studies finding that left-sided amygdala volume loss is greater than right (though it is actually the case that even this is present only at trend level at this stage of illness) (Vita *et al*. 2006). It would thus be expected that in a population such as ours (in which the putative process of transition to schizophrenia is in its early stages), any amygdala volume reductions associated with symptoms which are detectable would be on the left side.

The idea that structural brain abnormalities may precede frank psychosis is not new. Indeed, the basic premise for this study was that there may be a subgroup of learning disabled individuals whose cognitive impairment is due to a schizophrenic illness yet to become manifest as psychotic symptoms. Though interpretation is limited to those with mild/borderline intellectual impairment rather than more severe impairment, the current findings expand on this. They suggest that those intellectually impaired subjects at elevated risk of developing schizophrenia have abnormally large amygdalae. Within this population, however, there is an association between smaller amygdalae and more negative symptoms. Though follow-up is of course required, it seems likely that the risk of developing schizophrenia is even higher for these individuals with smaller amygdalae. If these are the individuals who do go on to develop schizophrenia, then it may be that these are further characteristics which can be used to refine models designed to predict the risk of schizophrenia developing in an individual.

Acknowledgements

We are deeply grateful to the participants and their families for their generous assistance. We thank the staff at the Division of Pyschiatry involved in recruiting the sample and those at the Scottish Higher Education Funding Council Brain Imaging Research Centre. This research was funded by a United Kingdom Medical Research Council Programme Grant awarded to E.C.J. T.W.M. was funded as part of this grant. S.M.L. was supported by the Sackler Foundation. K.H. was funded by a BMA grant to A.C.S.

Declaration of Interest

None.

References

Achenbach TM (1991). *Integrative Guide for the 1991 CBCL/4-18, YSR, and TRF Profiles*. Department of Psychiatry, University of Vermont: Burlington, VT.

Bonnici HM, Moorhead TWJ, Stanfield AC, Harris JM, Owens DG, Johnstone EC, Lawrie SM (2007). Pre-frontal lobe gyrification index in schizophrenia, mental retardation and comorbid groups: an automated study. *NeuroImage* **35**, 648–654.

Borgwardt SJ, McGuire PK, Aston J, Berger G, Dazzan P, Gschwandtner U, Pfluger M, D'Souza M, Radue E-W, Riecher-Rossler A (2007). Structural brain abnormalities in individuals with an at-risk mental state who later develop psychosis. *British Journal of Psychiatry* **191** (Suppl.), S69–S75.

Chance SA, Esiri MM, Crow TJ (2002). Amygdala volume in schizophrenia: post-mortem study and review of magnetic resonance imaging findings. *British Journal of Psychiatry* **180**, 331–338.

Convit A, McHugh P, Wolf OT, de Leon MJ, Bobinski M, De Santi S, Roche A, Tsui W (1999). MRI volume of the amygdala: a reliable method allowing separation from the hippocampal formation. *Psychiatry Research: Neuroimaging* **90**, 113–123.

Cooper SA, Smiley E, Morrison J, Williamson A, Allan L (2007). Mental ill-health in adults with intellectual disabilities: prevalence and associated factors. *British Journal of Psychiatry* **190**, 27–35.

Cunningham Owens DG, Johnstone EC (1980). The disabilities of chronic schizophrenia – their nature and the

factors contributing to their development. *British Journal of Psychiatry* **136**, 384–395.

Doody GA, Johnstone EC, Sanderson TL, Owens DG, Muir WJ (1998). 'Pfropfschizophrenie' revisited. Schizophrenia in people with mild learning disability. *British Journal of Psychiatry* **173**, 145–153.

Duvernoy H (1999). *The Human Brain: Surface, Three-Dimensional Sectional Anatomy with MRI, and Blood Supply*. Springer-Verlag: New York.

Grossberg S (2000). The imbalanced brain: from normal behavior to schizophrenia. *Biological Psychiatry* **48**, 81–98.

Gur RE, Loughead J, Kohler CG, Elliott MA, Lesko K, Ruparel K, Wolf DH, Bilker WB, Gur RC (2007). Limbic activation associated with misidentification of fearful faces and flat affect in schizophrenia. *Archives of General Psychiatry* **64**, 1356–1366.

Honea R, Crow TJ, Passingham D, Mackay CE (2005). Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *American Journal of Psychiatry* **162**, 2233–2245.

Hassiotis A, Ukoumunne O, Tyrer P, Piachaud J, Gilvarry C, Harvey K, Fraser J (1999). Prevalence and characteristics of patients with severe mental illness and borderline intellectual functioning. Report from the UK700 randomised controlled trial of case management. *British Journal of Psychiatry* **175**, 135–140.

Johnstone EC, Cosway R, Lawrie SM (2002). Distinguishing characteristics of subjects with good and poor early outcome in the Edinburgh High-Risk Study. *British Journal of Psychiatry* **181** (Suppl.), S26–S29.

Johnstone EC, Ebmeier KP, Miller P, Owens DGC, Lawrie SM (2005). Predicting schizophrenia: findings from the Edinburgh High-Risk Study. *British Journal of Psychiatry* **186**, 18–25.

Johnstone EC, Owens DGC, Hoare P, Gaur S, Spencer MD, Harris J, Moffat V, Brearley N, Miller P, Lawrie SM, Muir WJ (2007). Schizotypal cognitions as a predictor of psychopathology in adolescents with mild intellectual impairment. *British Journal of Psychiatry* **191**, 484–492.

Kapur S (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *American Journal of Psychiatry* **160**, 13–23.

Kay SR, Fiszbein A, Opler LA (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin* **13**, 261–276.

Kendler KS, Lieberman JA, Walsh D (1989). The Structured Interview for Schizotypy (SIS): a preliminary report. *Schizophrenia Bulletin* **15**, 559–571.

Lawrie SM, Abukmeil SS (1998). Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *British Journal of Psychiatry* **172**, 110–120.

Lawrie SM, McIntosh AM, Hall J, Owens DGC, Johnstone EC (2008). Brain structure and function changes during the development of schizophrenia: the evidence from studies of subjects at increased genetic risk. *Schizophrenia Bulletin* **34**, 330–340.

Lawrie SM, Whalley HC, Abukmeil SS, Kestelman JN, Donnelly L, Miller P, Best JJK, Owens DGC, Johnstone EC (2001). Brain structure, genetic liability, and psychotic symptoms in subjects at high risk of developing schizophrenia. *Biological Psychiatry* **49**, 811–823.

Lawrie SM, Whalley HC, Job DE, Johnstone EC (2003). Structural and functional abnormalities of the amygdala in schizophrenia. *Annals of the New York Academy of Sciences* **985**, 445–460.

Miller PM, Byrne M, Hodges A, Lawrie SM, Johnstone EC (2002). Childhood behaviour, psychotic symptoms and psychosis onset in young people at high risk of schizophrenia: early findings from the Edinburgh High Risk Study. *Psychological Medicine* **32**, 173–179.

Moorhead TWJ, Job DE, Whalley HC, Sanderson TL, Johnstone EC, Lawrie SM (2004). Voxel-based morphometry of comorbid schizophrenia and learning disability: analyses in normalized and native spaces using parametric and nonparametric statistical methods. *NeuroImage* **22**, 188–202.

Moorhead TWJ, Stanfield A, Spencer M, Hall J, McIntosh A, Owens DC, Lawrie SM, Johnstone EC (in press). Progressive temporal lobe grey matter loss in adolescents with schizotypal traits and mild intellectual impairment. *Psychiatry Research: Neuroimaging*.

Morgan VA, Leonard H, Bourke J, Jablensky A (2008). Intellectual disability co-occurring with schizophrenia and other psychiatric illness: population-based study. *British Journal of Psychiatry* **193**, 364–372.

Muir WJ, Davidson C, Doody GA (1998). A complex re-arrangement of karyotype involving chromosomes 2 and 11 detected in a patient with dual diagnosis of schizophrenia and mild learning disability. *American Journal of Medical Genetics* (*Neuropsychiatric Genetics*) **81**, 552–553.

Nacewicz BM, Dalton KM, Johnstone T, Long MT, McAuliff EM, Oakes TR, Alexander AL, Davidson RJ (2006). Amygdala volume and nonverbal social impairment in adolescent and adult males with autism. *Archives of General Psychiatry* **63**, 1417–1428.

Niemi LT, Suvisaari JM, Tuulio-Henriksson A, Lönnqvist JK (2003). Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. *Schizophrenia Research* **60**, 239–258.

Pruessner JC, Li LM, Serles W, Pruessner M, Collins DL, Kabani N, Lupien S, Evans AC (2000). Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. *Cerebral Cortex* **10**, 433–442.

Sanderson TL, Best JJK, Doody G, Owens DGC, Johnstone EC (1999). Neuroanatomy of comorbid schizophrenia and learning disability: a controlled study. *Lancet* **354**, 1867–1871.

Schumann CM, Hamstra J, Goodlin-Jones BL, Lotspeich LJ, Kwon H, Buonocore MH, Lammers CR, Reiss AL, Amaral DG (2004). The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. *Journal of Neuroscience* **24**, 6392–6401.

Shenton ME, Dickey CC, Frumin M, McCarley RW (2001). A review of MRI findings in schizophrenia. *Schizophrenia Research* **49**, 1–52.

Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S, Lawrie SM (2008*a*). Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. *European Psychiatry* **23**, 289–299.

Stanfield AC, Moorhead TWJ, Harris JM, Owens DGC, Lawrie SM, Johnstone EC (2008*b*). Increased right prefrontal cortical folding in adolescents at risk of schizophrenia for cognitive reasons. *Biological Psychiatry* **63**, 80–85.

Turner TH (1989). Schizophrenia and mental handicap: an historical review, with implications for further research. *Psychological Medicine* **19**, 301–314.

Velakoulis D, Wood SJ, Wong MTH, McGorry PD, Yung A, Phillips L, Smith D, Brewer W, Proffitt T, Desmond P, Pantelis C (2006). Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Archives of General Psychiatry* **63**, 139–149.

Vita A, De Peri L, Silenzi C, Dieci M (2006). Brain morphology in first-episode schizophrenia: a meta-analysis of quantitative magnetic resonance imaging studies. *Schizophrenia Research* **82**, 75–88.

Wechsler D (1992). *Wechsler Intelligence Scale for Children – III*. Psychological Corporation: New York.

Wechsler D (1999). *Wechsler Adult Intelligence Scale – III*. Psychological Corporation: New York.

WHO (1992). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Description and Diagnostic Guidelines*. World Health Organization: Geneva.

Wright IC, Rabe-Hesketh S, Woodruff PWR, David AS, Murray RM, Bullmore ET (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry* **157**, 16–25.