# Negative symptoms and longitudinal gray matter tissue loss in adolescents at risk of psychosis

Negative symptoms and longitudinal gray matter tissue loss in adolescents at risk of psychosis: preliminary findings from a 6-year follow-up study.

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**Declaration of interest**
None.

Abstract

**Background**

Negative symptoms are perhaps the most disabling feature of schizophrenia. Their pathogenesis remains poorly understood and it has been difficult to assess their development over time with imaging techniques.

**Aims**

To examine, using tensor-based structural imaging techniques, whether there are regions of progressive gray matter volume change associated with the development of negative symptoms.

**Method**

43 adolescents at risk of psychosis were examined using magnetic resonance imaging and whole-brain tensor-based morphometry at two time points, 6 years apart.

**Results**

When comparing the individuals with significant negative symptoms with the remaining participants, we identified 5 regions of significant gray matter tissue loss over the 6-year period. These regions included the left temporal lobe, the left cerebellum, the left posterior cingulate and the left inferior parietal sulcus.

**Conclusions**

Negative symptoms are associated with longitudinal gray matter tissue loss. The regions identified include areas associated with all psychotic symptoms, but also include regions uniquely associated negative symptoms.

## Introduction

Schizophrenia remains a major cause of disability, with substantial personal and economic costs. Classically the clinical features of schizophrenia are divided into positive symptoms and negative symptoms. Despite the clinical presentation being a mixture of both domains, it is the positive symptoms of the disorder which largely form the basis of the operationalised diagnostic criteria for schizophrenia (1, 2), which show a response to antipsychotic medication (3) and which have proven most tractable to research regarding their pathophysiology (4, 5). However, the negative symptoms of schizophrenia are arguably more disabling (6) and as yet there is no form of treatment which can be recommended as reliably relieving them (7). Advances in the development of new treatments for negative symptoms are hampered by a lack of understanding of their pathophysiology. A primary reason for this is that negative symptoms tend to emerge later rather than earlier in the course of schizophrenia (8) making it unusual for them to be ratable in a situation uncontaminated by confounding factors (9). Principal among these confounders is antipsychotic medication - it has long been known that negative features may be difficult to distinguish from antipsychotic-induced akinesia (10). Other features associated with long-term psychotic illnesses, such as depression (11), institutionalization (12) and social isolation (13), also complicate the clinical picture in those with longstanding illness.

In the Department of Psychiatry in Edinburgh we have focused upon the development of psychotic illness and as such have examined populations at enhanced risk of schizophrenia. Firstly we studied people where enhanced risk was familial (14), where we saw very little in terms of negative symptoms but this was not unexpected given the aims of the sample. We have gone on to examine individuals at enhanced risk for cognitive reasons (15, 16) and this is the sample used here. It is established that in people who are cognitively impaired, the risk of psychosis is higher (17), the onset earlier (18) and that negative symptoms are more marked (19) meaning that the current sample is particularly suitable for their longitudinal investigation in the absence of the confounding factors associated with chronic illness. A number of cross-sectional studies have previously reported associations between negative symptoms in schizophrenia and tissue loss, in particular gray matter tissue loss bilaterally in the insula, superior temporal gyrus and amygdala/hippocampus; as well as the left superior temporal gyrus, medial temporal gyrus and occipital gyrus (20-22). Conversely, other studies have reported decreased tissue loss associated with negative symptoms (23, 24). However, the assessment of negative symptoms in these studies is potentially confounded by the factors mentioned above. Therefore, the ability to assess negative symptoms repeatedly and in conjunction with serial scans in a substantial population, largely free from neuroleptic medication and at a much earlier age than in most other studies,

allows us the unusual opportunity to examine the correlates of negative symptoms developing over time in this at risk population.

## Methods

### Recruitment

A full description of the recruitment and design of the Edinburgh Study of Comorbidity (from which this sample comes) is published elsewhere (15). In brief, local Education Authorities in Scotland were approached for permission to approach individual schools. Of the 19 authorities approached, 18 granted permission. 243 schools across Scotland were subsequently approached and pupils receiving special educational assistance estimated to be functioning at a level consistent with borderline to mild intellectual disability were approached. After exclusions, 394 participants were recruited to undergo further study. After screening the group with the childhood behavior checklist (25) and the structured interview for schizotypy (26), and sampling the group based on these scores to enrich the cohort for participants with higher scores on these measures, 168 were recruited for the baseline MRI assessment (mean age 15.7 years). Of these, 120 consented to be re-contacted for a follow-up scan 6 years later. At follow-up, we successfully re-contacted 105 families of whom 55 agreed to participate in our follow-up imaging.

### Clinical Assessment

The Clinical Interview Scale (CIS) (27, 28) was used at each of the assessments with the examinations being conducted by the same raters on each occasion. In addition, the participants were assessed on the Positive and Negative Syndrome Scale (PANSS) (29) rated on the basis of this interview.

Using previously defined thresholds (16), the participants were divided into two groups using the scores in the negative symptoms subscale of the PANSS representing the presence or absence of morbid negative symptoms in this population. Individuals were allocated to the negative symptoms group if they had a score of 3 or above on any of the items of the negative subscale at either time-point, with the exception of *concrete thinking* and *lack of spontaneity and flow of conversation*. Most participants scored above a 1 on these items by virtue of their intellectual impairment therefore we considered a score of 4 to represent definite morbidity. However, none of the participants was allocated to the negative symptoms group solely on the basis of their scores in either *concrete thinking* or *lack of spontaneity and flow of conversation*. All but 6 participants provided DNA samples to exclude diagnoses of Down Syndrome, Fragile X Syndrome or Velocardiofacial Syndrome.

Image acquisition and pre-processing

The MRI data were collected using a 1.5T GE Signa Horizon HDX (General Electric, Milwaukee, WI). Following midline sagittal localization, the whole

brain was imaged by two further sequences: a transverse spin-echo scan acquiring both T2- and proton density-weighted images; and a coronal gradient echo sequence acquiring 128 high resolution coronal T1-weighted images for structural image analysis (time of inversion = 600 msec, echo time = 3.4 ms, flip angle = 15°, field of view = 220 mm, slice thickness = 1.7 mm, matrix = 256 × 192).

The images were converted to ANALYZE 3D format and each image was examined for orientation and movement artefacts. The images were analysed in SPM5 [www.fil.ion.ucl.ac.uk] running in MATLAB version 7.3 (The MathWorks, Natick, MA). The images were pre-processed using the SPM toolset before implementing the staged TBM protocol (30-33) to evaluate the gray matter tissue changes between the scans. For all scan acquisitions in this study we employed the same scanner, the same sequence and the same head coil. Nine participants were excluded from further analysis because of excess movement in the scans.

TBM Analysis

The TBM protocol was implemented by following a staged procedure (31, 32) and this was based on the established voxel-wise TBM methodology (30, 33). The TBM method is susceptible to participant movement during scan time. As a

result of this susceptibility we were not able to use the paired scans from eight of the participants. Also, one participant did not complete the scan sequence. For each of the participants we recovered grey matter difference images in MNI space from the TBM protocol.

The TBM grey matter difference images were smoothed with a 12-mm FWHM filter and compared in SPM using the general linear model (GLM). Comparisons were made between those with threshold negative symptoms and those without such features. Age, inter-scan time interval, sex, full scale IQ and PANSS positive symptom score were included in the model as covariates. The SPM t-contrast was initially thresholded at t=3.00 (uncorrected) but we report results only where the cluster significance corrected for multiple comparisons was $p<0.05$. Removal of the covariates from the SPM cluster analysis increased the extent of the reported clusters and established that our analyses including covariates were conservative. The TBM-VBM whole brain analysis was implemented in MNI standard space and the voxel co-ordinates of the results are presented in the same. The anatomical designations were taken from established atlases (34, 35).

Extracted values for whole brain gray matter volume were also compared to establish whether there was a relationship between change in volume and symptom states over time.

## Results

### Description of Participants

Of the 55 participants scanned at baseline and 6-year follow-up, 46 had paired scans of sufficient quality to allow for the TBM analysis. Three further participants were excluded, as their lack of communication at baseline did not make it possible to make an assessment of negative symptomatology. Of these 43 participants there were 13 females and 30 males, of mean age 15.6 years (s.d. 1.8) at baseline and 21.6 years (s.d. 1.8) at follow-up, and a mean IQ of 79.6. All participants either lived in their own home or in the family home at the time of the study. Of the participants, 5 were in further education, 4 in voluntary employment and 20 in paid employment, with the remainder being unemployed.

Table 1 shows the participants' characteristics as divided into the two clinical groupings. In general, the population was naïve to psychotropic medication but two of them were on antipsychotic medication: one who had developed operationally-defined schizophrenia since the beginning of the study and who was on depot flupentixol, lamotrigine and fluoxetine; the other participant was on small doses of amisulpiride and reboxetine for prominent anxiety symptoms. Both of these participants were in the negative symptoms group. A further two individuals, both in the non-negative symptom group were taking anti-depressant medication (sertraline and citalopram).

TABLE 1 HERE

At baseline, the group as a whole had a mean PANSS negative subscale score of 10.6 (SD=2.6), and at follow-up a mean score of 11.8 (SD=4.6). Figure 1 shows the median PANSS negative subscale scores for the two groups at both baseline and 6-year follow-up. The negative symptom scores do not differ significantly at baseline ($p=0.069$), though in the negative symptoms group are significantly higher at follow-up ($p<0.001$). There was no significant difference in scores of *observed depression* on the Clinical Interview Scale at baseline ($p=0.363$).
At baseline, five participants met our threshold for negative feature pathology, of whom four had ongoing morbid negative symptoms at follow-up. In addition to these, a further four had developed threshold negative symptoms at 6-year follow-up.

FIGURE 1 HERE

TBM Analysis

The whole-brain TBM analysis found a number of clusters of significantly greater gray matter tissue loss between the scans at baseline and 6-year follow-up in those with negative symptoms, compared to those who had not. These clusters were in the occipital, inferior parietal and medial temporal lobes, as well as the posterior cingulate and the cerebellum. The significance levels for these clusters were calculated using the SPM non-stationary toolbox. Figures 2a-e

show the location and extent of these clusters. There were no regions of significantly greater tissue loss in the participants without negative symptoms when compared to the group with those symptoms.

FIGURES 2a – 2e HERE

When the TBM analysis was repeated after excluding the two individuals on antipsychotic medication, the left medial temporal gyrus and left cerebellum results remained significant. However, the other 3 results no longer remained significant. A third, new cluster in the cerebellum, however, did emerge as significant. The location of the maximal voxel for this cluster (T=3.78) was at MNI co-ordinates (-6 -68 -38).

Whole Brain Gray Matter Volumes

Figure 3 shows the results from our analysis of whole brain gray matter volumes over time. The differences between the groups are not significant at baseline (p=0.881) or follow-up (p=0.858), nor is the change over time (p=0.591).

FIGURE 3 HERE

Discussion

In this study we undertook serial MRI brain imaging of young individuals with intellectual limitations, scanning them at mean ages 16 and 22. Between these two time points, we found clusters of significantly greater gray matter tissue loss in the individuals with prominent negative symptoms compared to those without prominent negative symptoms. This included areas of greater tissue loss in the posterior cingulate, cerebellum, superior temporal gyrus, medial temporal lobe and occipital lobe all on the left hand side. The groups did not differ significantly in terms of positive symptoms at either baseline or follow-up, nor were any of the participants institutionalised. The neuroanatomical changes over time that we report are therefore likely to relate to the presence of negative symptoms in this group and not to other confounding factors. One potential confounder is that although this group is almost completely antipsychotic naïve, particularly when compared to other study populations, nonetheless, two of the individuals in the negative symptoms group were on antipsychotic medication. During further TBM analysis in which we excluded these individuals, two of the results remained significant and a new, significant result was found. We cannot know whether the loss of the significant results in the left superior temporal gyrus, left occipital lobe and left posterior cingulate is due to the absence of antipsychotic effect or merely due to the smaller sample size but we can be sure that the development of negative symptoms in a sample uncontaminated by antipsychotic medications is associated with tissue loss in the left cerebellum and the left medial temporal gyrus.

To the authors' knowledge this is the first longitudinal study in a group at high risk of psychosis due to cognitive reasons to relate structural changes to increasing negative symptom severity. Within this group we have previously demonstrated gray matter tissue loss in the bilateral medial temporal lobes and superior temporal gyri to be associated with significant levels of positive and negative symptoms considered together (16) (Table 2). The results of the current study overlap with these previous findings in relation to left medial temporal and superior temporal gyrus gray matter loss, but we also identified tissue loss in the left posterior cingulate, left cerebellum and left occipito-parietal region as uniquely associated with negative symptoms. Each of these regions has been previously reported to be associated with deficits in social cognition, which is known to be impaired in individuals with prominent negative symptoms (36).

TABLE 2 HERE

In the current study we reported a large region of tissue loss at 6-year follow-up in the left posterior cingulate, which is consistent with the findings of a previous cross-sectional study of individuals with schizophrenia (37). It is possible that this finding may help the understanding of the nature of the specific deficits of

negative symptoms. The posterior cingulate plays an important role in the default mode network (38) and negative symptoms have been previously reported to be correlated with decreased connectivity between the posterior cingulate and various brain regions including frontal, temporal and midbrain structures (39) as well as gray matter tissue loss in the posterior cingulate in individuals with schizotypal personality disorder (40). Theory of mind activity (the ability to attribute mental states to others) has also been linked to increased activity in the posterior cingulate (41) and it is, therefore, of interest that we have found significant tissue loss in this area associated with prominent negative symptoms, which have been associated with deficits in theory of mind (42). Our finding suggests that this may be an area prone to tissue loss early in the course of a developing illness, and that tissue losses may be observable prior to the onset of illness and be involved in the aetiology of the disabling and treatment-refractory negative symptoms.

Our TBM results of tissue loss in the inferior parietal lobule are consistent with results from previous studies of negative symptoms in patients with schizophrenia (43, 44) and support the idea of the involvement of the inferior parietal lobule in the development of schizophrenia. This is in keeping with the hypothesised role of mirror neurons in the inferior parietal lobule with regard to social cognition, specifically empathy and understanding the actions and intentions of others (45, 46). An alternative possible explanation is that it may

relate to the importance of the parietal lobe in functions which are disturbed in schizophrenia such as spatial working memory, language and attention (47).

Although more known for its role in motor co-ordination the cerebellum is increasingly recognised as having a variety of non-motor functions including a role in social cognition (48). Therefore, our finding of significant tissue loss in the left posterior cerebellum, which has previously been shown to be the region most associated with non-motor deficits (49), is in keeping with the evidence of its role in theory of mind as it relates to negative symptoms.

It is not clear to what degree prominent negative symptoms herald the development of schizophrenia, although it has previously been suggested that negative symptoms form an earlier, rather than later, part of the prodromal illness (50). However, when combined with the finding of Hazlett et al that decreased superior temporal gyrus volumes were found in individuals with schizophrenia compared to those with schizotypy (51), suggests that prominent negative symptoms and gray matter changes may indeed be the forbearer of a threshold illness.

Study Limitations

There are certain limitations to this study. Firstly, the group with negative symptoms are slightly but significantly older than those without. This is not

unexpected as the older subjects are closer to the peak age of onset of schizophrenia. However, as age was included as a covariate in the TBM analysis we know that the age difference does not explain our main results. Secondly, while it could be suggested that in the negative symptoms group we are merely looking at a group with more severe illness, and while in terms of negative symptoms this is clearly the case, it is not so in terms of positive symptoms which do not differ (see table 1). It is possible that the negative symptoms are a precursor to the development of manifest psychosis but this transition has yet to occur.

The number of individuals with negative symptoms is relatively small and confirmation in a larger sample would be desirable. However, the sample from which this group was derived was very large (15, 16) and the opportunity of observing the development of negative symptoms over time in a group as large as this is unusual. The significance of the negative symptoms in terms of their role as a precursor of the development of schizophrenia cannot be known at this stage. Finally, the inclusion of two individuals in the non-negative group who were taking anti-depressants is a possible confounder, although amongst the group of 34, of whom the other 32 were medication free, we think it unlikely that this was driving the results. In addition the measures of *observed depression* at baseline did not differ significantly between the groups.

## Conclusion

The presence and development of negative symptoms in people at high risk of schizophrenia for cognitive reasons is related to gray matter tissue loss in brain regions associated with social cognition. Our findings compliment and add to those of previous studies in groups at increased risk for other reasons (e.g. genetic high risk or clinical high risk). As noted, the pathophysiology of negative symptoms has been poorly understood and effective treatments have been hard to find. The results presented here do not overcome these problems but may represent a first step towards meaningful understanding of the biological underpinnings of these disabling symptoms of schizophrenia.

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