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Title Page

Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies

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Abstract

Background: Lateral ventricular enlargement is one of the most consistent findings in patients with schizophrenia; however whether progressive ventricular dilation occurs during the course of the illness has been controversial. To clarify this we conducted a meta-analysis of longitudinal studies measuring the lateral ventricles in patients with schizophrenia and a control group.

Methods: The MEDLINE database was searched from 1980-2009 for longitudinal MRI studies of patients with schizophrenia. We identified 13 studies that measured the lateral ventricles in both patients and controls and these were included in a random effects meta-analysis. The effect of various clinical variables was investigated in a meta-regression analysis.

Results: Patients showed evidence of progressive ventricular enlargement after illness onset greater than that seen in controls (Effect size=0.45, 95%CI 0.19-0.71, $p=0.0006$). A sub-analysis of chronic patients with schizophrenia with a mean duration of illness of 7.6 years at baseline scan also showed progressive ventricular enlargement ($p=0.002$). The results were robust to inclusion criteria, and no significant effect of age of onset, duration of illness, or age at baseline scan, was found in the meta-regression analysis.

Conclusions: The meta-analysis shows progressive changes in ventricular volume a number of years after illness onset and challenges an exclusively neurodevelopmental model of schizophrenia.

Keywords: MRI, schizophrenia, meta-analysis, longitudinal, progressive, ventricle

INTRODUCTION

The presence of structural brain abnormalities in schizophrenia is well established (Vita, et al. 2006; Wright, et al. 2000); however the concept of progressive change, which may indicate neurodegeneration, is controversial (DeLisi 2008; Weinberger and McClure 2002). A number of MRI studies have reported changes in brain structure over time in patients with schizophrenia, however the findings appear inconsistent and the regions studied frequently differ (DeLisi and Hoff 2005; Kasai, et al. 2003). To clarify these findings, we carried out a meta-analysis of lateral ventricular volume change in longitudinal MRI studies of patients with schizophrenia and control subjects. Although there have been a number of meta-analyses of cross-sectional MRI studies in schizophrenia (Steen, et al. 2006; Vita, et al. 2006; Wright, et al. 2000), to our knowledge this is the first meta-analysis of longitudinal studies. We selected the lateral ventricles because cross-sectional meta-analyses have repeatedly reported large effect sizes for ventricular dilation (Vita, et al. 2006; Wright, et al. 2000), and this region has also been consistently measured in longitudinal studies. We hypothesised that patients with schizophrenia would show progressive dilation of the lateral ventricles over time compared to controls. In terms of moderating variables we predicted that studies with a longer interscan interval would show greater volume increases.

METHODS AND MATERIALS

Study selection

Our strategy in the meta-analysis was to use broad inclusion criteria, and to examine the effect of more selective criteria in the sensitivity analysis. Thus the initial inclusion criteria for the meta-analysis were peer-reviewed studies which measured the lateral ventricles or entire ventricular system in the brain at a minimum of two time points using Magnetic Resonance Imaging (MRI) in a group of patients with schizophrenia and a control group. We also included studies which combined patients with schizophrenia with other psychotic disorders (schizoaffective disorder, schizophreniform disorder, and psychosis not otherwise specified). We excluded case studies, reviews, publications which had not used standard diagnostic criteria, and duplicate publications using the same sample of subjects. Studies using Computed Tomography (CT) were excluded to reduce study heterogeneity and because of the small number of CT longitudinal studies which included both patients and controls. The MEDLINE database was searched up to July 2009 using a combination of relevant Medical Subject Headings (MeSH); detailed search terms are available from the authors on request. Thirteen publications fulfilled the inclusion criteria (see figure 1).

Obtaining change and SD of change measures

To calculate the effect size for ventricular enlargement we required the change in volume from a baseline MRI scan to a follow-up MRI scan and standard deviation of change in the patient and control group. For studies where this was not available we

contacted the authors directly for these data. Where authors were unable to provide us with the data, and the results were presented graphically we measured these to obtain means and standard deviations (3 studies), (Degreef, et al. 1991; Nakamura, et al. 2007; Rapoport, et al. 1997). Graphs were measured digitally using the GNU imaging manipulation program (v2.6.1) measure tool (Mattis and Kimball 2008). Studies varied in how they reported the changes in volume. Nine studies reported volume change over the entire interscan interval and 4 studies reported mean annual volume change. Five studies reported volumetric change in millilitres (ml), 2 studies reported a percentage change in volume, and for 6 studies we had access to both ml and percentage change measures. Studies reporting changes in ml implicitly assume a linear growth of ventricular volume over time while studies reporting changes in terms of a percentage of the baseline measurement assume an exponential growth over time. In the main meta-analysis we included all 13 studies and calculated the effect size from volume changes in ml if this measure was available; if this measure was not available percentage change was used. To determine the validity of combining ml measurement with percentage change, we calculated the correlation coefficient between these measures for 6 studies where both measurements were given. The correlation was high both in the patient ($R=0.97$, $p<0.01$) and control group ($R=0.96$, $p<0.01$) suggesting the measures are comparable. However in addition to the main meta-analysis we also performed supplementary meta-analyses separating these two measures (see below).

Three studies reported change in ventricular volume for the left and right ventricle separately rather than total lateral ventricular change (DeLisi, et al. 1997; Mathalon,

et al. 2001; Whitworth, et al. 2005). To calculate the total ventricular change, the sum of the left and right volume change was taken. The standard deviation for total volume change was calculated from:

$$\sigma_T = \sqrt{\sigma_L^2 + \sigma_R^2 + 2\sigma_L\sigma_R\rho_{LR}}$$

where σ_T , σ_L and σ_R is the standard deviation change in volume for the total, left and right ventricle respectively and ρ_{LR} is the correlation coefficient between the left and right ventricle volume. For an estimate of ρ_{LR} we used the result of an independent study (Rao, et al. 2006) which reported a correlation coefficient of 0.78 between the left and right lateral ventricle. This technique has also been used in a recent meta-analysis (Koolschijn, et al. 2009).

Two studies presented measures from subgroups of patients rather than a combined patient group. For these studies we entered the subgroups into the meta-analysis as if they were separate studies and in each case the number of subjects in the control group was the sample size of the control group divided by the number of patient subgroups. This technique has also been used in a previous meta-analysis (Kempton, et al. 2008). One study reported lateral ventricle volumes using both coronal and axial oriented MRI scans (DeLisi, et al. 1997). In this case we selected the coronal MRI scans as the majority of studies included in the meta-analysis used this orientation.

Combining study estimates

Outcome measures were recorded from each study and were re-checked on a second occasion by the same investigator (MJK) to ensure accuracy. Hedges g was used as the effect size for each study, which is Cohen's effect size d with a correction

for bias from small sample sizes (Hedges and Olkin 1985). The definition of hedges g is,

$$g = \left(1 - \frac{3}{4(n_p + n_c) - 9} \right) \frac{x_p - x_c}{\sigma_{pc}}$$

where x_p and x_c is the change in volume in the patient group and control group respectively, σ_{pc} is the pooled standard deviation of the change measures in the patient and control group, and n_p and n_c are the numbers of subjects in the patient and control group respectively.

The standardised effect sizes were subsequently pooled using a random-effects inverse weighted variance model, (DerSimonian and Laird 1986). The true effect is assumed to have a normal distribution in the population of studies, and the aim of the random effects model meta-analysis is to estimate the mean of this distribution. Random effects models generally produce wider confidence intervals and are more conservative than fixed effects models. The meta-analyses were performed in STATA 9.2 (StatCorp 2006) using the *METAN* command (Bradburn, et al. 1998).

Assessing between-study heterogeneity

The heterogeneity of effect sizes was assessed formally by applying Cochran's q test for homogeneity (Sutton 2000) and informally by assessing a sample size independent descriptive measure of inconsistency I^2 (Higgins, et al. 2003). The I^2 measure describes the percentage of total variation across studies that is due to heterogeneity of the effect sizes. I^2 ranges between 0 (no inconsistency) and 100%

with values of 25%, 50% and 75% suggested as low, moderate and high heterogeneity.

Publication bias

Publication bias may be assessed by visually inspecting a funnel plot, which displays a measure of study precision against study effect size. We used Egger's regression test which is a formal method of assessing publication bias (Egger, et al. 1997) as implemented with the STATA function *METABIAS* (Steichen 1998).

Subgroup meta-analyses

A meta-analysis of outcome measures of first-episode patients who were scanned at baseline (4 studies) was computed and compared to a meta-analysis of patients with chronic schizophrenia at baseline (8 studies). One study reported outcome measures separately for first episode and chronic patients; the results from these subgroups were included in each meta-analysis as appropriate. To compare the effect sizes from the two patient groups a Z-test was used. As studies reported results in terms of ml and percentage change, we also performed two separate meta-analyses for these measures.

Exploratory meta-regression of clinical variables

The effects of clinical variables were assessed in a random effects meta-regression model by using the *METAREG* (Sharp 1998) command in STATA 9.2. The default option using residual maximum likelihood (REML) was selected. As the meta-

regression was exploratory and 7 variables were investigated, results were considered significant if they passed a Bonferroni corrected p-value <0.007 .

Sensitivity analysis

To test how robust the results were to variations in the meta-analysis methodology, we examined the effect of the following on the meta-analysis estimate, a) excluding 3 studies which combined schizophrenia with other psychotic disorders, b) excluding 2 studies which had measured the entire ventricular system rather than the lateral ventricles only, c) excluding 3 studies where we had obtained an effect size from measuring graphical data, d) changing the correlation coefficient between the left and right ventricle volume to 0.1 and 1, and e) repeating the meta-analysis 13 times each time excluding one study.

RESULTS

Main meta-analysis

The meta-analysis comprised 13 studies with a total of 473 patients and 348 control subjects (see table 1 and 2). Patients with schizophrenia and psychotic disorders showed increased rates of lateral ventricle dilation over time compared to controls (13 studies, Effect size $g=0.449$, 95%CI 0.192-0.707, $p=0.0006$), see figure 2. There was significant moderate to high between-study heterogeneity ($I^2=63\%$, $Q=37.3$, $p<0.001$) and no evidence of publication bias ($p=0.27$).

Subgroup meta-analyses

First episode patients compared to chronic patients

When the meta-analysis was restricted to studies of first episode patients (as assessed at baseline) there was a similar effect size to the main meta-analysis although this was not significant (5 studies, mean age of onset=25.5, mean interscan interval=2.1 years, Effect size $g=0.491$, 95%CI -0.113 to 1.095, $p=0.11$). In a meta-analysis of studies of chronic patients, significant progression was found (9 studies, mean duration of illness at baseline scan=7.6 years, mean age of onset=19.6, mean interscan interval=3.7 years, Effect size $g=0.407$, 95%CI 0.134 to 0.679, $p=0.003$). There was no significant difference in effect size between studies which scanned first episode patients at baseline versus patients with chronic illness (Difference in effect size $g=0.08$, 95%CI -0.542 to 0.711, $p=0.79$).

Studies reporting a fixed volume change

In a sub-analysis we only included studies which reported changes in absolute volume (ml) over time (11 studies). Patients with schizophrenia and psychotic disorders showed increased rates of lateral ventricle dilation in terms of absolute volume change over time compared to controls (Effect size $g=0.320$, 95%CI 0.101 to 0.540, $p=0.004$). There was significant moderate between-study heterogeneity ($I^2=43%$, $Q=21.1$, $p=0.049$) and no evidence of publication bias ($p=0.60$). The ratio of mean volume change in patients per year to the mean volume change in controls per year was 2.9.

Studies reporting a percentage volume change

When the effect size was calculated from percentage change in ventricular volume over time (8 studies), patients with schizophrenia and psychotic disorders showed increased rates of lateral ventricle dilation compared to controls (Effect size $g=0.646$, 95%CI 0.220 to 1.071, $p=0.003$). There was significant moderate to high between-study heterogeneity ($I^2=67%$, $Q=21.1$, $p=0.004$) and no evidence of publication bias ($p=0.64$). The ratio of the mean percentage volume change in patients per year to the mean percentage volume change in controls per year was 4.3.

Exploratory meta-regression of clinical variables

There was no significant association (Bonferroni corrected $p<0.007$) between the following variables and study effect size: mean patient interscan interval (13 studies, $p=0.49$), mean patient age at baseline scan (13 studies, $p=0.79$), percentage of female patients (11 studies, $p=0.27$) mean duration of illness at baseline scan (13

studies, $p=0.61$) and mean age of onset (13 studies, $p=0.31$). In addition there was no association between the percentage of patients using typical (5 studies, $p=0.50$) or atypical neuroleptic medication (5 studies $p=0.31$) and study effect size. A meta-regression examining the effects of medication dosage was not possible as only 3 studies reported dosage in terms of chlorpromazine equivalents. However 6 of the 13 studies examined correlations between ventricular volume change and medication dosage and/or compliance. Four of these reported no significant correlation and 2 studies reported correlations showing that medication compliance was associated with a *slowing* of ventricular enlargement (DeLisi, et al. 1997; Nair, et al. 1997). In terms of other within-study correlations, 5 studies reported that progressive ventricular enlargement was associated with a significantly poorer outcome or higher symptom score (Ho, et al. 2003; Lieberman, et al. 2005; Nakamura, et al. 2007; Rapoport, et al. 1997; van Haren, et al. 2008). We did not identify any other consistent correlations from individual studies.

Sensitivity analysis

The result of the main meta-analysis remained significant (Effect size $g=0.29$ to 0.52 , all $p<0.003$) when we a) excluded studies which had recruited patients with psychotic disorders other than schizophrenia, b) excluded studies which measured the entire ventricular system rather than the lateral ventricles only c) excluded studies where effect sizes were calculated from graphical data, d) entered a correlation coefficient between the left and right ventricle volume as 0.1 and 1, or e) repeated the meta-analysis 13 times each time excluding one study.

DISCUSSION

In this meta-analysis we have shown that lateral ventricular volume continues to increase in patients with schizophrenia after illness onset. The ratio of patient to control changes in volume, suggest that the increase observed in patients is approximately 3 to 4 times that observed in normal aging. In a sub-analysis, progression of ventricular volume was also found in chronic patients who had been ill for an average of 7.6 years. We did not find significant ventricular progression in patients with first episode schizophrenia, although it is likely that this analysis was underpowered as only 5 studies were available. In addition the effect size for first episode patients ($g=0.49$) was comparable to the main analysis ($g=0.45$) suggesting that progression may also occur early in the illness. In the meta-regression analysis we did not find any relation between progression in lateral ventricular volume and interscan interval or other clinical variables.

There was a wide variation of ventricular change observed both within and between studies. Although robust, an effect size of $g=0.45$ indicates there is overlap in rates of progression between patients with schizophrenia and controls, and that a minority of patients show *less* progression than the control group mean. Large neuroimaging studies may reveal if there are distinct subgroups of patients, some of whom show progression, and others who show no change in ventricular volume. Although preliminary, our examination of within study correlations suggest that a progressive course may be associated with poorer outcome.

Evidence for schizophrenia as a neurodevelopmental disorder is consistent with a number of findings in patients with schizophrenia such as minor physical anomalies (Weinberg, et al. 2007), neurological soft signs (Chan, et al. 2009), reduced brain asymmetry (Sommer, et al. 2001) and an increased rates of obstetric complications (Geddes, et al. 1999). Static volumetric deficits in brain structure have been cited as supporting the neurodevelopmental hypothesis of schizophrenia so progressive changes are problematic to an exclusively neurodevelopmental theory. However in terms of our meta-analysis supporting a neurodegenerative process, it is important to stress that neuropathological studies argue against conventional neurodegeneration (Harrison and Weinberger 2005) and that MRI cannot measure neurodegeneration directly. Nonetheless these findings deserve further investigation by post-mortem studies and novel positron emission tomography (PET) tracers (Zhou, et al. 2009) which may be able to elucidate the mechanism of progressive volume change.

Interestingly, changes in ventricular volume may be more strongly associated with environmental than genetic factors. Cross-sectional studies show a strong influence of the environment on ventricular volume in both healthy controls (Baare, et al. 2001) and patients with schizophrenia (McNeil, et al. 2000). In addition one longitudinal study of twin pairs discordant for schizophrenia has suggested that progressive changes in ventricular volume are associated with nonshared environmental effects (Brans, et al. 2008).

Are progressive changes an effect of medication?

Although studies in first episode patients suggest that ventricular enlargement per se is not a direct result of medication (Steen, et al. 2006; Vita, et al. 2006), it is difficult to separate the effect of medication and chronic illness on *progressive* changes in ventricular volume. Nearly all patients with schizophrenia over a period of one or more years would be medicated, and testing the effects of neuroleptics on brain structure in healthy controls over a long period is clearly not ethical. A study in macaque monkeys found that both haloperidol and olanzapine were associated with decreased brain weight compared to a control group, suggesting antipsychotic medication may affect brain structure (Dorph-Petersen, et al. 2005). Conversely pneumoencephalographic studies in the earlier 1900's, before the advent of antipsychotic medication, reported ventricular progression (Moore, et al. 1935). Although such early reports were methodologically less rigorous than current MRI studies, they suggest that progressive changes are not a result of medication. In addition, for studies included in this meta-analysis, the only significant correlations of medication compliance and ventricular change suggested medication *slows* ventricular dilation.

Why did early CT studies not detect progressive changes in ventricular volume?

Early cross-sectional CT studies in schizophrenia did not consistently find a correlation between duration of illness and ventricular volume (Weinberger, et al. 1979), and most CT longitudinal studies could not find a progressive change in volume (Nasrallah, et al. 1986; Vita, et al. 1988), a notable exception being the study by Davis et al. (Davis, et al. 1998). Based on these earlier studies, it was concluded by

some researchers that ventricular volume was static after illness onset. However early CT longitudinal studies used less sensitive measures than those available today to quantify brain structure, many quantifying ventricular size from only one scan slice for analyses. In addition nearly all CT studies included less than 25 patients suggesting these studies were underpowered to detect the small change in volume over time. From the effect size calculated in this meta-analysis a longitudinal study would be required to recruit 63 patients and 63 controls ($\alpha=0.05$, $\text{power}=0.8$) and a less powerful cross sectional study would require considerably more subjects. Weinberger and McClure (2002) have criticised longitudinal MRI studies, stating that there is too much variation between study results, impossibly large changes in brain volume, and that other factors could explain the findings such as medication, alcohol and substance abuse, and non-stimulating environments. We agree that inter-study heterogeneity is high, although this is common in both the neuroimaging and psychiatry literature and likely due to different patient populations, imaging methodologies and analysis techniques. Performing a random effects meta-analysis allows this to be taken into account and provides an estimate of inter-study variability. The heterogeneity index of 63% in this meta-analysis is comparable to values seen in our previous meta-analysis of cross sectional MRI studies in bipolar disorder (Kempton, et al. 2008) which varied from 0% to 91% depending on the brain structure analysed. It is true that some longitudinal studies report large changes in volume and this may have been caused by scanner and outlining changes between the baseline and follow-up scan, however by using effect sizes in the meta-analysis this issue is circumvented by taking into account the change in the control group. At this stage we cannot discount confounding variables such as alcohol and substance

abuse and unstimulating environments, although our analysis of within study correlations suggest that medication compliance does not increase ventricular progression.

Limitations

A limitation of this study is that only ventricular volumes have been analysed. In this initial meta-analysis we chose the lateral ventricles due to the robust difference between patients and controls observed in cross-sectional studies, and because a large number of longitudinal studies have measured this region. In the meta-regression analysis we were limited to analysing variables which were consistently reported in the individual studies, thus we were unable to examine measures which may influence progressive changes such as specific medications, unstimulating environments and co-morbid conditions. Although the case control meta-analysis is statistically high powered the meta-regression analysis of clinical variables is low powered and may be prone to type II errors. Large, well controlled longitudinal studies may be able to examine these variables more effectively.

When does ventricular enlargement start in schizophrenia?

Six different trajectories in ventricular volume in patients with schizophrenia are illustrated (figure 3). Although not exhaustive, the graphs demonstrate popular models including variations of the neurodevelopmental and neurodegenerative hypotheses. The results of this meta-analysis and other studies can be used to select the most likely trajectory. In our meta-analysis we have shown that there are progressive changes in ventricular volume in patients with schizophrenia, which

would eliminate models a), c) and e). In addition meta-analyses of first episode patients with schizophrenia show that there are enlarged ventricles at illness onset (Steen, et al. 2006; Vita, et al. 2006), suggesting that model d) is incorrect. Thus we speculate that the true trajectory in patients with schizophrenia is either model b) an abnormal brain developmental process that begins close to birth with progressive changes throughout life, or model f) progressive changes starting in the prodromal phase of the illness. The trajectories may also be modulated by psychotic episodes and periods of remission (Garver, et al. 2000), although we were unable to examine this in the meta-analysis, as the majority of studies reported data from two time points only. It should be noted that the rate of progression is based on an average from the studies included in the meta-analysis, and may not be valid for ages and durations of illness outside the ranges reported by studies incorporated in the meta-analysis. Prospective longitudinal studies of children at genetic high-risk for schizophrenia and those beginning at least if not premorbid, in the prodromal stage of illness will be required to determine which is the most likely trajectory between b and f. Such studies would also reveal whether progressive change occurs even before clinical illness begins, what its lifetime course is, and whether the timing of changes varies among individuals with the same clinical disease.

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FIGURE LEGENDS

Figure 1 Title: Flow chart showing study selection for the meta-analysis

Figure 2 Title: Meta-analysis forest plot of longitudinal changes in ventricular volume in patients with schizophrenia compared to controls.

Figure 2 legend: The effect size is shown for each study with the pooled effect size indicated by the gray diamond. Error bars are 95% confidence intervals and the effect size is Hedges g which is Cohens' d with an adjustment for small sample sizes.

Abbreviations: Olz=Olanzapine, Hal=Haloperidol, FE=First Episode, ME=Multiple Episode

Figure 3 Title: Schematic of lateral ventricle volume trajectories over the lifetime in patients with schizophrenia compared to control subjects

Figure 3 legend: Six proposed trajectories are shown. In each graph the horizontal axis is age and the vertical axis is lateral ventricular volume in ml. The mean trajectory of healthy controls and patients with schizophrenia is indicated by the black and red curve respectively. Mean age of onset of schizophrenia is indicated by the dashed vertical line. The control curve is for illustrative purposes but is based on the 3 studies covering a combined span of birth-80 years (Giedd, et al. 1996; Knickmeyer, et al. 2008; Marcus, et al. 2007). The trajectories are divided into non-progressive and progressive models (left, right) and at what time dilation starts (top, middle and bottom). The results of this meta-analysis and meta-analyses of patients with first episode schizophrenia argue for trajectory b) or f) (see discussion).

Table 1

Study	Diagnosis	No. Patients	No. Controls	Mean interscan interval for patients (years)	Mean patient age at baseline scan	Mean duration of illness at baseline scan (years)
Degreef et al. 1991	RDC schizophrenia	13	8	1.25	25.1	First episode
DeLisi et al. 1997	SADS schizophrenia (n=33), schizoaffective disorder (n=8), psychosis NOS (n=2), other (n=6)	50	20	4.7	27.4	First episode
Nair et al. 1997	DSM-IV schizophrenia (n=13) schizoaffective (n=4) psychosis NOS (n=1)	18	5	2.58	30.4	8.6
Rapoport et al. 1997	DSM-III-R schizophrenia	16	24	2.23	14.8	4.6
Mathalon et al. 2001	DSM-III-R schizophrenia	24	25	3.6	39.4	15.3
Puri et al. 2001	DSM-IV schizophrenia	24	12	0.59	28.5	First episode
Saijo et al. 2001	DSM-III-R schizophrenia	15	12	10	37.5	15.1
James et al. 2002	DSM-III-R schizophrenia	16	16	2.71	16.6	2
Ho et al. 2003	DSM-IV schizophrenia	73	23	3.3	24.5	3
Lieberman et al. 2005	DSM-IV schizophrenia, schizophreniform, schizoaffective disorder	73	44	1	23.8	1.2
Whitworth et al. 2005	DSM-III-R schizophrenia	38	20	1	26.5	3.9
Nakamura et al. 2007	DSM-III-R schizophrenia	17	26	10.45	24.7	First episode
van Haren et al. 2008	CASH schizophrenia	96	113	1.67	32.2	11
Mean (SD)	-	36.4 (27.8)	26.8 (27.7)	3.5 (3.2)	27.0 (7.0)	7.2 (5.5)

Abbreviations: RDC=Research Diagnostic Criteria, SADS=Schedule of Affective Disorders and Schizophrenia, CASH= Comprehensive Assessment of Symptoms and History

Table 2

Study	Mean Change in ml (SD)		Mean Percentage change (SD)	
	Patients	Controls	Patients	Controls
Degreef et al. 1991	-1.05(2.05)	-0.08(1.17)	-4.47(9.78)	-0.24(7.26)
DeLisi et al. 1997	0.31(0.41)	0.13(0.38)	5.58(6.70)	1.50(7.65)
Nair et al. 1997	2.18(1.65)	0.76(0.56)	22.1(16.4)	8.80(8.78)
Rapoport et al. 1997	3.32(3.29)	-0.21(0.16)	24.5(29.6)	0.16(16.10)
Mathalon et al. 2001	1.60(2.47)	0.72(1.32)	NA	NA
Puri et al. 2001	0.59(2.03)	0.04(0.55)	NA	NA
Saijo et al. 2001	NA	NA	22.9(18.7)	5.10(15.00)
James et al. 2002	0.63(1.54)	0.22(1.02)	4.13(7.36)	2.51(9.89)
Ho et al. 2003	0.78(2.43)	0.30(1.13)	5.69(15.46)	2.45(9.13)
Lieberman et al. 2005	Olz group 0.37(3.56) Hal group 0.37(3.17)	0.34(1.72)	NA	NA
Whitworth et al. 2005	FE group 0.29(0.57) ME group 0.16(0.38)	0.14(0.16)	NA	NA
Nakamura et al. 2007	NA	NA	10.45(7.67)	1.03(3.34)
van Haren et al. 2008	1.67(2.88)	1.02(1.80)	NA	NA

Abbreviations: Olz=Olanzapine, Hal=Haloperidol, FE=First Episode, ME=Multiple

Episode, NA=Data not available

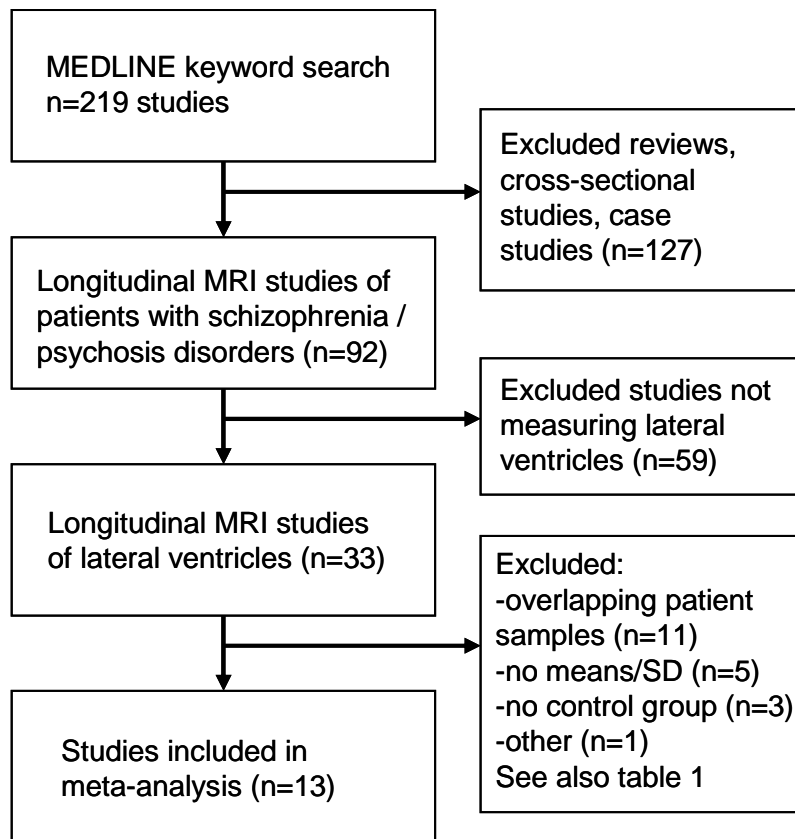


Figure 1

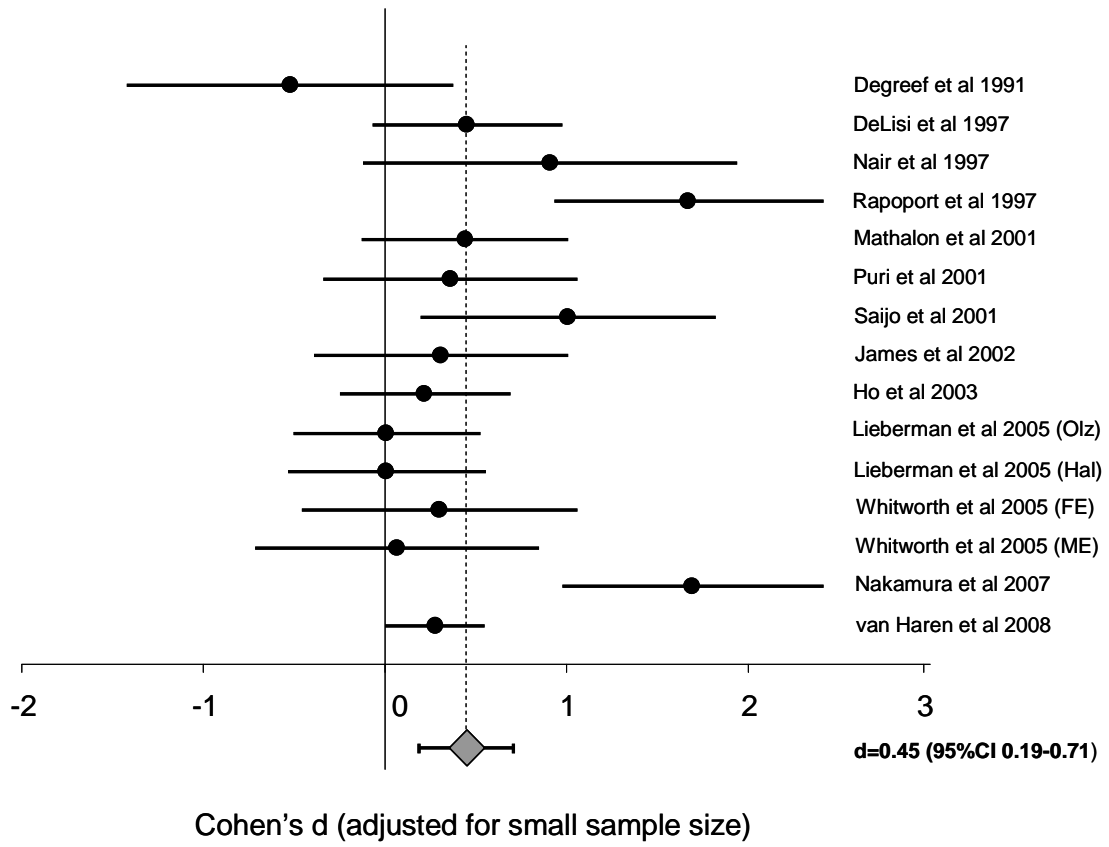


Figure 2

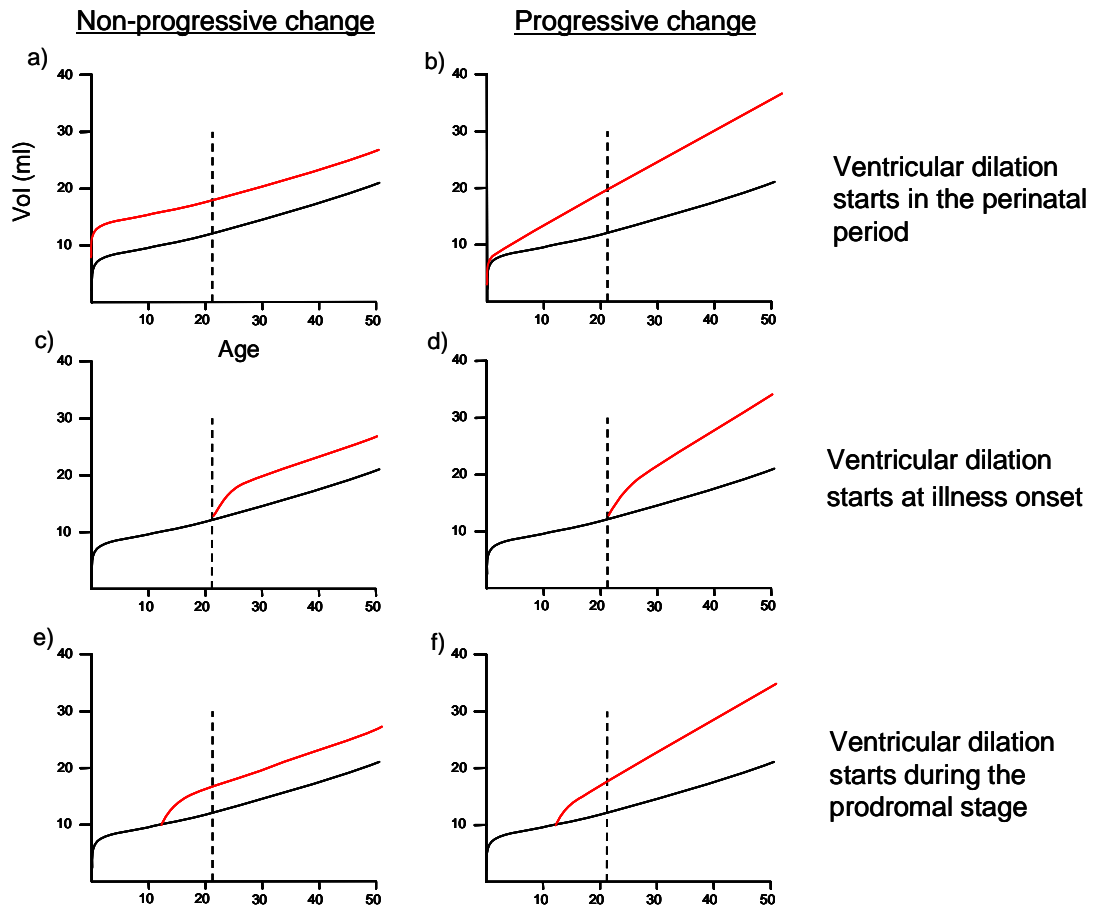


Figure 3