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REVIEW ARTICLE

Does active psychosis cause neurobiological pathology? A critical review of the neurotoxicity hypothesis

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Background. Since the neurotoxicity hypothesis was launched in 1991, it has generated a great deal of interest and given rise to several studies investigating the validity of the hypothesis that being psychotic has a toxic effect on the brain. The toxicity argument is used to justify early treatment. This review attempts to assess the studies that have addressed the question: Does an active psychosis, indexed by the duration of untreated psychosis (DUP), cause neurobiological pathology?

Method. The validity of the hypothesis has been studied primarily by correlation analyses that assess whether there are significant correlations between DUP and changes in neurocognitive functioning or brain structure. In this review, relevant reports were identified by a literature survey.

Results. Of the 35 studies (33 papers) evaluated, six neurocognitive studies supported the hypothesis and 16 did not. Eight morphology studies supported the hypothesis and five did not. In general, the studies that did not support the neurotoxicity hypothesis were larger in size and had more adequate designs (longitudinal) than those that supported the hypothesis.

Conclusions. Overall, there is limited empirical evidence for the neurotoxicity hypothesis in the studies reviewed. However, it is possible that there is a threshold value for a toxic effect of psychosis, rather than a linear relationship between DUP and a neurotoxic effect, and that several of the studies evaluated did not have a long enough DUP to detect a toxic effect of active psychosis.

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Introduction

In 1991, in a review of the effects of neuroleptic drugs on the course of schizophrenia, Richard Wyatt asked: 'Is there something about being psychotic that is toxic to the individual beyond the immediate psychotic episode?' (Wyatt, 1991, p. 347). Wyatt found that early intervention in first-onset schizophrenia patients increased the likelihood of an improved long-term course, and based on the association between the duration of untreated psychosis (DUP) and outcome, he hypothesized that psychosis may be biologically toxic to the brain.

Sheitman & Lieberman (1998) postulated that neurotoxicity develops after sustained overstimulation of neurons, thereby suggesting a three-stage model of the pathophysiological processes that underlie the disease pathogenesis and progression. An endogenous neurochemical sensitization, resulting from an inability to regulate a presynaptic dopamine release in the limbic striatum, may in the last stage result in a response refractoriness in schizophrenia patients. This last stage involves the development of structural neuronal changes consequential to prolonged sensitization.

It has also been proposed that an active psychosis may be neurotoxic by reducing neuronal connectivity (Goldberg *et al.* 2009). Moreover, it is conceivable that an active psychosis leads to the experiencing of stress and the release of stress-related hormones, both of which can affect functional and structural changes in the brain (Wood *et al.* 2009).

There has been continuous interest in this hypothesis during the past two decades. One of the reasons for this interest may be that the neurotoxicity hypothesis has been used to support the view that it is important to receive early drug treatment because an untreated psychosis may be harmful to the brain. Some have even advocated that people at high risk of developing schizophrenia should be medicated. A Cochrane

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review by Marshall & Rathbone (2011) concluded that there is emerging evidence that people in the prodrome of psychosis can be helped by interventions.

Several studies have addressed the neurotoxicity hypothesis. McGlashan (2006) provided a theoretical review of the question, 'Is active psychosis neurotoxic?' He argued that certain manifestations in the further course of the illness would be expected if an active psychosis was indeed neurotoxic, and claimed that there is little evidence for any such manifestations. The present paper is the first systematic review of relevant empirical studies to assess the validity of the hypothesis.

Whether DUP is causally related to, or a marker of, poorer outcomes remains unclear (McGlashan, 2006). To prove the causality in the hypothesis that untreated psychosis causes damage to the brain, more than correlational designs are needed. Testing a causal hypothesis requires disproving the alternative hypothesis that a person who is neurobiologically vulnerable to a severe form of schizophrenia develops the disease in ways that lead to later detection and treatment. Research designs that could test a causal hypothesis would require the prospective prediction of schizophrenia caseness, in addition to long-term follow-up of a large prospective birth cohort sample (McGlashan, 2006). No such study has been carried out; hence, the investigations to rely on when assessing the validity of the neurotoxicity hypothesis are studies with a correlation design.

The reports that have been used to substantiate or reject the hypothesis are studies in which functional or structural brain data have been correlated with DUP. Those that have found significant associations between DUP and deficits in functional or structural brain functions have been taken as evidence that untreated psychosis has a toxic effect. Conversely, studies that have found no such correlations have been taken as not supporting the hypothesis.

Quantitative meta-analysis has become the most common approach for assessing overall effects in multiple studies that have examined the same issue. In the present review, a meta-analytic approach was not deemed suitable for several reasons: first, there was considerable variation with respect to measures, neuropsychological (NP) tests and brain areas in the different reports. Second, only a few observations were made in many of the studies, which would probably result in substantial random fluctuations in effect size measures. The major problem, however, is that for many of the studies in which no statistically significant associations between DUP and neurocognitive/morphological variables were found, sufficient data for a meta-analysis were not reported. For example, non-significant effects are usually reported without any further detail. Trying to disentangle the possible sources of variability in effect size measures by a formal quantitative meta-analysis, given these restrictions, was not considered informative. A systematic review was judged to be a more appropriate approach.

As a backdrop for an assessment of the hypothesis, we know that there is an extensive amount of empirical evidence that functional and structural brain changes occur before the onset of illness and continue after the debut of the psychosis (Rund, 2009; Olabi *et al.* 2011). A neurodevelopmental disturbance probably begins perinatally, and continues pre-morbidly, prodromally and after the onset of psychotic symptoms. The question in relation to the neurotoxicity hypothesis is rather whether active psychotic symptoms accelerate the damage to the brain.

The question asked in this review is: Assessing all relevant studies in which functional or structural brain data have been correlated with DUP, what is the empirical evidence for the hypothesis that active psychosis, as indexed by DUP, causes damage to brain functions or structure?

Method

We aimed to identify all studies available where the neurotoxicity hypothesis had been addressed empirically. Only studies in which functional or structural brain data were correlated with DUP have been included because only these have addressed the neurotoxicity hypothesis empirically. Relevant reports were identified by a literature survey using the search terms 'schizophrenia', 'psychosis', 'neurotoxicity', 'neurocognition', 'morphology' and 'DUP'. All the terms were combined in separate surveys. A database search was performed on PubMed/Medline, PsycINFO and the Web of Science. To include all relevant papers, regardless of publication date, no date specification of the search criteria was used; the relevant papers identified were those published between 1998 and 2013. Additionally, the articles found during these search procedures were studied for relevant citations, and a few relevant publications came to our attention in other ways. With respect to neurocognition, a minimum requirement for inclusion was that NP tests were applied. For instance, Scully *et al.* (1997) was excluded from the review because cognitive function was not assessed by NP tests. Similarly, studies with very heterogeneous diagnostic samples of psychoses were excluded. Thus, the study of Lawoyin *et al.* (2007) was excluded because their sample included several diagnoses outside the schizophrenia spectrum, among them substance-induced psychosis. In total, 33 papers of relevance were found, with two of them including both neurocognitive and morphological measures.

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The papers were assessed against the following methodological issues: (*a*) Is the research design cross-sectional or longitudinal? (*b*) Is there a sufficient number of participants? (*c*) Is DUP adequately defined? (*d*) Is DUP long enough to expect any toxic effect? (*e*) Are the number of significant associations greater than would be expected by chance given the number of correlations computed? (*f*) Were the patients treated with antipsychotics?

Results

Neurocognitive studies supporting the hypothesis (Table 1a)

Amminger *et al.* (2002) provide limited support for the view that psychotic symptoms might be neurotoxic. An association between DUP and an estimate of cognitive deterioration was reported. When symptoms were included in the regression model, DUP ceased to be statistically significant. Furthermore, an untreated psychosis of up to 4 weeks showed no signs of cognitive deterioration.

The study by Joyce *et al*. (2002) is an expansion of the Barnes *et al*. (2000) study and has several limitations, including no criteria-based definition of DUP. A robust association between DUP and attentional set-shifting ability was found. Patients who failed the test had a mean DUP that was almost twice as long as those who passed. However, this was the only task that correlated significantly with DUP. This study should therefore be seen as a very limited confirmation of the neurotoxicity hypothesis.

Lappin *et al.* (2007) provide a well-designed examination with adequate DUP criteria. The study lends some support to the prediction that a longer DUP is associated with a poorer neurocognitive ability in schizophrenia participants at first presentation. However, several neurocognitive domains were not associated with DUP. In addition, significant associations between DUP and verbal learning and verbal working memory at the time of the first episode disappeared after correction for age, gender, education and ethnicity. Only the association with IQ remained significant. The authors interpret their findings as supporting the conclusion that impairments in neurocognitive function lead to a longer DUP through delayed effective help-seeking, while also pointing out that a longer DUP may be the result of other poor prognostic factors.

Gaynor *et al.* (2009) found that the length of DUP predicted neurocognitive deterioration. When DUP was assessed in three categories, only one significant difference was found in the level of neurocognitive deterioration between the group with DUP <1 month and the group with DUP >6 months. The authors interpret this finding as an indication that there may be a potential treatment window for neurocognitive deterioration. If DUP is reduced to <6 months, the risk of significant cognitive deterioration may also be reduced. The study has several limitations, including unclear DUP criteria.

Chang *et al.* (2013) provide supportive evidence that delayed treatment of first-episode psychosis is associated with poorer cognitive outcome. They examined patients in a longitudinal design and found that memory deficits were the most related to DUP. Prolonged DUP was associated with more severe impairments in verbal memory at both 24- and 36-month follow-up assessments.

The cross-sectional study of Zhou *et al.* (2012) of first-episode schizophrenia patients and healthy controls found DUP to have an adverse effect on prospective memory.

Neurocognitive studies not supporting the hypothesis (Table 1b)

In general, the study of Barnes *et al.* (2000) does not support the hypothesis. However, very limited evidence of an association between DUP and neurocognitive function was found. When DUP was split around the median, patients in the long DUP group performed worse on an attentional task at a trend level of significance.

In Hoff *et al.* (2000), estimates of DUP were reached by a consensus of two researchers after independent review of all records, which was probably not a very reliable method. Statistical analyses were carried out with DUP as both a continuous and a dichotomous variable, with 1 year as the cut-off point. No significant correlations were found between measures of untreated illness and the severity of neurocognitive deficits at baseline. The authors conclude that the study provides no support for the hypothesis that a period of untreated illness is toxic to the brain.

Norman *et al.* (2001) found no relationship between DUP and performance on any component of an extensive battery of cognitive tests. One significant correlation appeared between DUP and an index of neurocognitive deterioration. The correlation was negative, suggesting that less deterioration is associated with longer periods of active untreated psychosis. The authors suggest that this finding could reflect the ability of individuals with less deterioration to function for longer periods without treatment, which contradicts the hypothesis of psychosis having toxic effects.

In the study of Townsend *et al.* (2002), DUP was not related to the degree of change in cognitive functioning. One limitation of this study is that symptom

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Table 1. *Associations between duration of untreated psychosis (DUP) and neurocognitive measures in patients with psychosis*

(*a*) *Studies supporting the neurotoxicity hypothesis*

Study	Subject	NP measures	Design and follow-up	DUP (days) Mean/S.D.	Results
Amminger *et al.* 2002	42 schizophrenia, FE	WAIS-R	Assessment at clinical stabilization DUP: three categories	246/525	Longer DUP predicted cognitive deterioration. When symptoms were included in the regression model, DUP ceased to be statistically significant. DUP did not affect all cognitive domains equally
Joyce *et al.* 2002	136 schizophrenia, FE	NP tests: CANTAB test of memory and executive functions	DUP: no criteria. Established for each patient by reviewing relevant information	No information	Only performance on an attentional set-shifting task correlated with $\log_{10}$ DUP, indicating that the shorter the DUP, the higher the stage reached
Lappin *et al.* 2007	180 schizophrenia, FE	Broad NP battery	NP assessment at enrollment DUP: from onset of psychosis to first contact with mental health service DUP: four categories	427/931	Long DUP was associated with impaired performance in verbal IQ, verbal learning and verbal working memory. Only the IQ association remained significant when corrected for age, gender, education and ethnicity
Gaynor *et al.* 2009	50 psychosis, FE	WAIS-III DI calculated	NP assessment when patients symptomatically stable Unclear DUP definition DUP: three categories	519/1167	DUP predicted cognitive deterioration. When DUP was assessed with the three categorical groups, only one significant difference was found in the level of cognitive deterioration between < 1 month and > 6 months
Chang *et al.* 2012	93 schizophrenia, FE	NP battery	Prospective 3-year follow-up DUP: time interval between onset of positive symptoms and treatment initiation	474/768	Prolonged DUP was associated with more severe impairments in visual memory at clinical stabilization and verbal memory at 24 and 36 months. No significant main between-subject effect of DUP on other cognitive measures was found
Zhou *et al.* 2012	51 schizophrenia, FE	NP battery Cambridge Prospective Memory Test	Cross-sectional Unclear DUP definition	396/351	Longer DUP contributed to poorer performance on both time- and event-based prospective memory

(*b*) *Studies not supporting the neurotoxicity hypothesis*

Study	Subject	NP measures	Design and follow-up	DUP (days) Mean/S.D.	Results
Barnes *et al.* 2000	53 schizophrenia, FE	NP battery CANTAB	NP tests within 3 months after entering study DUP: onset of psychosis to antipsychotic medication DUP: two categories	413/651	The only difference between the long and short DUP group emerged on a set-shifting task. This performance was worse in the longer DUP group at a trend level of significance
Hoff *et al.* 2000	50 schizophrenia, FE	Comprehensive NP battery	NP tests within 1 month after stabilization with neuroleptics DUP: review of records; two categories (<1 year and >1 year)	342/486	No significant correlations were observed between measures of untreated illness and cognitive deficits at baseline. The study provides no support for the hypothesis that a period of untreated illness is toxic to the brain
Norman *et al.* 2001	113 psychosis, FE	Extensive battery of cognitive tests	Early intervention program DUP: period from initial onset of psychosis to treatment	438/?	Only one significant correlation was found between a cognitive performance index and DUP, namely verbal IQ. This was negative, suggesting less deterioration being associated with longer periods of active untreated psychosis
Townsend *et al.* 2002	83 schizophrenia spectrum	Broad NP battery	A cumulative DUP measure. DUP defined as: time of onset of first psychotic symptoms until 1 month of treatment or significant symptom reduction	Median: 168	Results did not support any effect of DUP on change in scores for any of the cognitive measures
Ho *et al.* 2003	156 schizophrenia, FE	36 NP test variables grouped into nine cognitive domains	DUP defined as time period from the onset of full positive syndrome to the initiation of neuroleptic treatment	520/1016	No correlations between neurocognitive functioning and DUP reached statistical significance. When DUP was divided into two groups based on the median, only one significant difference was found between the long and short DUP groups, namely on verbal memory
Addington *et al.* 2004	164 psychosis, FE	Broad NP battery	NP assessed at admission, 12 months and 24 months DUP: length of time from first positive symptom to first effective treatment	589/973	No associations were found between DUP and any of the cognitive tests at the initial, 12-month or 24-month follow-up
Heydebrand *et al.* 2004	307 schizophrenia, FE	Broad NP battery	NP assessed at baseline. Patients were recruited to participate in a clinical trial of antipsychotics DUI was calculated by subtracting date of initial treatment study visit from date of illness onset	657/1421	DUI prior to assessment was not significantly associated with cognitive impairment
Rund *et al.* 2004	207 psychosis, FE	Eight NP tests assessing five domains, plus three subscales of the WAIS-R	NP testing within 9 months after admission DUP: time from onset of psychotic symptoms to first adequate treatment of psychosis.	74/?	No significant associations were found between DUP and any of the cognitive domains in bivariate analyses. The same held for all eight specific tests
Galinska *et al.* 2005	30 schizophrenia, FE	Six NP tests	DUP not defined	Median: 70	No correlations found between neurocognitive function and DUP

Table 1 (*cont.*)

(*b*) *Studies not supporting the neurotoxicity hypothesis*

Study	Subject	NP measures	Design and follow-up	DUP (days) Mean/S.D.	Results
Ayres *et al.* 2007	179 psychosis, FE	NP tests: Verbal fluency Digit span forward Digit span backward	NP assessed when patients made contact with mental health services for the first time No clear definition of DUP (onset of psychotic phenomena to contact with mental health services)	265/1083	No associations found between cognitive performance indices and DUP
Rund *et al.* 2007	111 psychosis, FE	NP tests: see Rund *et al.* 2004	NP testing 1 year after baseline assessment and 2 years after baseline	Median: 56	No significant associations between any neurocognitive dimension and DUP
Galderisi *et al.* 2009	454 schizophrenia, FE	Broad NP battery	Cross-sectional; patients assessed at baseline Unclear DUP definition Exclusion: > 2 years of DUP	182/157	Patients performed worse than healthy controls on all NP tests. DUP was not associated with cognitive impairment
Goldberg *et al.* 2009	102 schizophrenia, FE	Comprehensive NP battery	DUP measured in two ways, from emergence of psychotic symptoms and of psychiatric symptoms	113/162	A relationship between longer DUP and worse cognition was not discerned, irrespective of whether DUP was treated as a continuous or a categorical variable
Leeson *et al.* 2010	53 psychosis, FE	WAIS A few NP tests	DUP: time period between the emergence of psychotic symptoms and treatment onset	No information	No statistically significant relationship
Cuesta *et al.* 2012	77 psychosis, FE	Comprehensive NP battery	Longitudinal study; patients assessed at baseline, 1 month and 6 months DUP evaluated by the SOS inventory	412/1231 (negative symptoms) 522/1190 (positive symptoms)	Mixed results. Patients with a short DUP outperformed patients with a long DUP on memory tasks and a pre-attentional task, but not on measures of verbal fluency, attention, reaction time, visual processing and executive functions
Rapp *et al.* 2013	60 psychosis, FE 24 at-risk subjects	Comprehensive NP battery	DUP: time period between first positive psychotic symptom and first contact with EDS DUI: time period between first self-perceived symptoms and first contact with EDS	1036/692	No significant correlations between DUP or DUI and outcome of NP tests or DI

FE, First episode; WAIS-R, Wechsler Adult Intelligence Scale – Revised; NP, neuropsychological; CANTAB, Cambridge Neuropsychological Test Automated Battery; WAIS-III, Wechsler Adult Intelligence Scale – Third Edition; DI, deterioration index; DUI, duration of untreated illness; SOS, Symptom Onset in Schizophrenia; EDS, early detection service; S.D., standard deviation.

reduction was clinically defined through an interview with the program staff.

Ho *et al.* (2003) carried out analyses with DUP as both a continuous and a dichotomized variable on the basis of median DUP (13 weeks). Only one significant difference was found between the long and short DUP group; for verbal memory. The absence of strong correlations suggests that untreated initial psychosis has no toxic effects. A strength of this study is the large study sample.

Addington *et al.* (2004) initially assessed neurocognitive functioning when psychosis patients were admitted to a psychosis program, and at 12- and 24-month follow-ups. No associations were found between the $\log_{10}$ DUP and any of the neurocognitive tests at any of the three assessments.

In the study by Heydebrand *et al.* (2004), schizophrenia patients who were recruited to participate in a clinical trial were assessed with a comprehensive NP battery at baseline before assignment to a double-blind treatment. Duration of untreated illness (DUI), the time period from the date of the onset of illness to the date of the initial treatment study visit, was not significantly associated with cognitive impairment.

Rund *et al.* (2004) assessed a large number of first-episode psychosis patients with an NP battery within 9 months of admission. No association was found between DUP and any neurocognitive dimension or specific tests.

Galinska *et al.* (2005) assessed a small sample of first-episode schizophrenia patients with six NP tests. DUP was not defined but is reported to be 10 weeks (median). No correlations between neurocognitive function and DUP were found.

Ayres *et al.* (2007) tested first-onset psychoses patients with three NP tests in a population-based study. The cognitive performance revealed no relationship to DUP.

In the study of Rund *et al.* (2007), 54% of the patients assessed at baseline (Rund *et al.* 2004) were reassessed 1 and 2 years later with the same NP battery. The median DUP was 8 weeks. Only data for the patients with follow-up at three points were included. No associations between neurocognitive functions and DUP were found. The authors concluded that neurocognitive functioning was an independent domain, not related to DUP.

Galderisi *et al.* (2009) examined a large study sample of 454 first-episode patients with minimal or no prior exposure to antipsychotics. DUP was not associated with cognitive impairment.

Goldberg *et al.* (2009) assessed schizophrenia patients with a NP battery at the study's entry point. DUP was measured in two ways: in weeks, from the emergence of psychotic symptoms to the initiation of pharmacological treatment and from the emergence of any psychiatric symptoms to pharmacological treatment. No relationship between longer DUP and worse neurocognition was discerned, irrespective of whether DUP was treated as a continuous or a categorical variable, or whether DUP was measured from the emergence of psychotic or psychiatric symptoms.

Although investigating the relationship between DUP and neurocognition was not among the research aims of the report by Leeson *et al.* (2010), where first-episode psychosis patients were examined on several cognitive variables, both variables were measured. No significant relationship was found between them.

Cuesta *et al.* (2012) assessed drug-naïve, first-episode patients with a NP battery at baseline, 1 month and 6 months. To assess the effect of DUP on the NP status of the patients, a linear mixed-effect model was fitted to each NP dimension. Patients with a short DUP outperformed patients with a long DUP on memory tasks and a pre-attentional task. On most NP dimensions, including measures of verbal fluency, attention, reaction time, visual processing and executive functions, a long DUP was not significantly related to levels of improvement in cognitive function. Because the results were mixed in this report, importance is not given to weighting for or against the neurotoxicity hypothesis.

The study of Rapp *et al.* (2013) included 60 first-episode psychosis patients and an at-risk mental state with later transition to psychosis (ARMS-T) sample of 24 subjects. Associations between DUP and neurocognitive performance were tested by three different operationalizations of cognition, among them a deterioration index (DI). No significant correlations were found between DUP and outcome of the NP tests or DI. However, longer DUP was significantly associated with stronger negative symptoms. It is suggested that no significant relationships between DUP and neurocognition were found because schizophrenic psychoses are neurodevelopmental disorders in which most cognitive deficits exist before the onset of symptoms.

Craig *et al.* (2000) reported no significant association between the 24-month illness course and outcome in 349 first-episode psychosis patients. The study is not included in this review because it lacked an adequate NP assessment.

Becker *et al.* (2010) and Hawkins *et al.* (2008) studied persons at ultra-high risk for psychosis. These two studies did not assess the association between DUP and neurocognition but give important support to the claim that psychosis does not result in neurocognitive deterioration. They found that persons who developed psychosis between two assessments of cognitive functioning did not perform significantly worse at

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the second assessment than at the first on any neurocognitive measure. This shows that the participants did not deteriorate cognitively after they had experienced their first psychotic episode, which gives no support to the neurotoxicity hypothesis.

Morphology studies supporting the hypothesis (Table 2a)

Keshavan *et al.* (1998) carried out magnetic resonance imaging (MRI) scans before and after 1 year of treatment, and in addition to the cerebellar volume, the superior temporal gyrus was the main area of interest. Both DUP and DUI were estimated. DUI was inversely related to the volume of the left superior temporal gyrus, a finding that was strictly confined to males. The authors conclude that it is possible that the untreated, early course of schizophrenia may be associated with progressive neurobiological deficits.

Madsen *et al.* (1999) examined the interaction of the clinical course in schizophrenia and brain structure with computerized tomography (CT) at first admission and 5 years later. The frontal enlargement at first admission depended on DUP, although this finding should be interpreted with caution because of the retrospective nature of the information about DUP. A limitation of this study is the method used to investigate brain structures.

Lappin *et al.* (2006) examined first-episode psychosis patients with high-resolution MRI and voxel-based methods of image analysis. A longer DUP was associated with gray matter reductions in the left middle and inferior temporal, left occipital and left fusiform cortices, and with gray matter excess in the left basal ganglia. The limitation observed in this study is that some of the patients were being treated with antipsychotics.

Caudate nucleus volumes were of primary interest in the study by Crespo-Facorro *et al.* (2007). Of note, no volumetric abnormalities were found in patients when compared to healthy controls. Both DUP and DUI were calculated. Patients with a longer DUP had a smaller caudate nucleus. A limitation is that patients had been treated prior to the MRI acquisition. Antipsychotics may have produced changes in the caudate brain volume, causing the observed association between DUP and a smaller caudate nucleus volume.

Takahashi *et al.* (2007) divided schizophrenia patients into long and short DUP groups based on the median DUP. There was a significant inverse correlation between DUP and the relative volume of gray matter in the left planum temporale, although other regions of interest (ROIs) did not correlate with DUP. A major limitation is that many of the patients were not assessed in their first episode, and some patients were medicated. There is increasing evidence that antipsychotic medication has an independent effect on brain morphology (Cahn *et al.* 2002).

The type of tissue of interest in the study by Bangalore *et al.* (2009) was gray matter. Both DUI and DUP were calculated. A significant inverse correlation was found between DUI and gray matter density in the left fusiforum gyrus, extending into the lingual gyrus and cerebellum. This finding was only seen in first-episode schizophrenia patients. DUI did not have any major effect on the brain structure of patients with other psychotic disorders.

Penttilä *et al.* (2010) examined a population-based sample with psychosis subjects with several years of illness. They were scanned using MRI after an 11-year follow-up. DUP was assessed from medical records and regressed against global and local tissue density measurements. DUP did not correlate with volumes of total gray or white matter or cerebrospinal fluid (CSF). However, DUP was positively associated with reduced densities in the right limbic area and the right hippocampus. This result was present after adjusting for several potential confounding and mediating factors. Hence, the findings were mixed, but are interpreted by the authors as supporting the hypothesis that a long DUP could be a marker of different disease trajectories, including subtle morphometric changes.

Gray matter, white matter and CSF were the types of tissue of interest in the study by Malla *et al.* (2011). DUP was divided into two: <18 weeks and >18 weeks. Gray matter volume reduction in the inferior-orbital region and parietal area in patients with long compared to short DUP is reported. In addition, a whole-brain gray matter volume reduction was found in the long DUP group. No differences were found between the two groups with regard to white matter or CSF.

Morphology studies not supporting the hypothesis (Table 2b)

Fannon *et al.* (2000) examined schizophrenia patients in their first episode of psychosis. ROIs in the MRI scans were whole brain volume, cortical gray matter, lateral ventricles and temporal lobes. The conclusions that can be drawn from this study concerning neurotoxicity are limited because the patient population was a mix of both treated and untreated patients. No associations were found between the duration of psychosis and regional brain volumes.

Hoff *et al.* (2000) conclude that there is no support for the hypothesis that a period of untreated illness is toxic to the brain structure or function. Fifty patients were examined on brain structure volumes. The ROIs

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in the MRI scans were the lateral ventricle, the central hemisphere and the temporal lobe. No statistically significant correlations were found between DUP and baseline brain structure volumetric measurements. Furthermore, no statistically significant differences were found between patients with <1 year and >1 year of untreated psychosis on any brain structure variable.

Malla *et al.* (2002) reported CT scan ratings of various aspects of brain morphology in a sample of first-episode schizophrenia patients, finding a modest enlargement of the sulci and ventricles and a reverse asymmetry of the sylvian fissure in comparison with a sample of patients with chronic schizophrenia. CT ratings were not related to DUP.

Hietala *et al.* (2003) examined a small sample of schizophrenic first-admission patients and concluded that DUP was not associated with measures of morphology.

Ho *et al.* (2003) examined schizophrenia spectrum patients with analyses of MRI scans, including volumetric measures of total brain tissue, gray and white matter and CSF, and measures of brain surface anatomy. DUP was treated as a continuous variable and was also divided into two groups on the basis of the median. No significant correlations or differences between groups were found, with the exception of one patient with a short DUP who had a significantly thicker sulcal cortical depth. The authors conclude that the absence of strong cortical relationships suggests that untreated initial psychosis has no toxic neural effect.

Discussion

Six neurocognitive studies supported the hypothesis; 16 did not. The studies supporting the hypothesis vary greatly in terms of quality and methodology. The study by Amminger *et al.* (2002) provides only weak support to the neurotoxicity hypothesis, suggesting that the correlation between symptoms and DUP is of greater importance than between neurocognition and DUP. By contrast, the study by Cuesta *et al.* (2012) lends some support to an association between DUP and memory, although an overall assessment suggests no support for the hypothesis. The studies that can be given importance as confirmation of the hypothesis are those by Lappin *et al.* (2007), Gaynor *et al.* (2009), Zhou *et al.* (2012) and Chang *et al.* (2013), all of which have a sufficient number of patients. However, only one of them (Chang *et al.* 2013) is longitudinal, and the significant relationships between DUP and neurocognitive variables are limited in number. In the study by Lappin *et al.* (2007), the correlation between IQ and DUP is the only robust finding whereas Gaynor *et al.* (2009) provide a certain support for the hypothesis, but only when the DUP is greater than 6 months.

There are numerous neurocognitive studies that do not provide any empirical support for the hypothesis. Many of them (Townsend *et al.* 2002; Addington *et al.* 2004; Rund *et al.* 2007; Cuesta *et al.* 2012) are longitudinal, and all have a sufficient number of patients. A comprehensive assessment suggests that, in general, the neurocognitive studies do not provide substantial support for the hypothesis.

When it comes to the morphology studies, the picture is not as clear. Eight studies supported the hypothesis, five did not. These studies are also difficult to assess, in part because there are progressive structural changes during the development of psychosis (Rund, 2009) that increase around the time of onset (Ziermans *et al.* 2010). Some of the studies have serious shortcomings. For instance, Keshavan *et al.* (1998) included the prodromal phase in addition to DUI, which makes it impossible to determine what has been added in structural changes after the onset of illness and what was present before psychosis onset.

Some morphology studies have a small number of patients (Keshavan *et al.* 1998; Hietala *et al.* 2003). Another problem is that ROIs have varied from one study to another, and different studies have found changes in different brain structures. Another limitation is that some studies included participants on antipsychotic medication (Crespo-Facorro *et al.* 2007; Takahashi *et al.* 2007). In addition, patients other than first-episode patients were included sometimes, thereby making it difficult to know when the structural changes took place. Lastly, the diagnostic criteria for inclusion vary between studies.

The studies that provide the clearest support for the hypothesis are those of Crespo-Facorro *et al.* (2007), Takahashi *et al.* (2007), Bangalore *et al.* (2009) and Malla *et al.* (2002), which all had sufficient numbers of participants and adequate DUP assessments and brain scanning techniques. These studies all found associations between DUP and restricted areas of the brain, including a smaller caudate nucleus (Crespo-Facorro *et al.* 2007), and a reduction in gray matter volume in the left planum temporale (Takahashi *et al.* 2007), gray matter density in the left fusiforum gyrus (Bangalore *et al.* 2009) and gray matter in the inferior-orbital region and parietal area (Malla *et al.* 2002).

The most serious challenges encountered in assessing these studies is that the morphological changes (e.g. gray matter loss) precede the onset of overt psychotic symptoms and that treatment with antipsychotics may affect brain structures. It is difficult to separate the changes that would have happened

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Table 2. *Associations between duration of untreated psychosis (DUP) and brain morphology in patients with psychosis*

(*a*) *Studies supporting the neurotoxicity hypothesis*

Study	Subject	Measures	Design and follow-up	DUP (days) Mean/S.D.	Results
Keshavan *et al.* 1998	17 schizophrenia, FE	MRI scans: the superior temporal gyrus was of primary interest; In addition: the cerebellar volume	MRI scans before and after 1 year of treatment. Both DUI and DUP were calculated. DUI included the prodromal phase	1211/1413	Concerning associations between DUI and regional brain volume measures, the volume of the left superior temporal gyrus was significantly related to DUI after partialling out the effect of intracranial volume. This relationship was only significant for males
Madsen *et al.* 1999	21 schizophrenia, FE	CT scans	CT scans performed at first admission and at reinvestigation 5 years later DUP was estimated retrospectively	No information	Significant power to distinguish patients with or without prefrontal sulcal enlargement was found from DUP
Lappin *et al.* 2006	81 psychosis, FE	High-resolution MRI	Cross-sectional design DUP estimated in a conventional way	77/105	Temporal gray matter reductions were more marked in patients with a long DUP
Crespo-Facorro *et al.* 2007	76 psychosis, FE	MRI scans. Caudate nucleus volumes of primary interest	MRI scanning before treatment Both DUI and DUP were calculated	333/543	No volumetric abnormalities were found in patients compared to healthy controls. Patients with a longer DUP had a smaller caudate nucleus
Takahashi *et al.* 2007	38 schizophrenia	ROIs: superior temporal subregions; medial temporal lobe structures; frontal lobe region	DUP defined as time from manifestations of first psychotic symptoms to neuroleptic treatment	198/321	A significant negative correlation between DUP and the volume of gray matter in the left planum temporale. No other correlations were found between DUP and the other brain regions. The long DUP group had significantly less planum temporale gray matter than the short DUP
Bangalore *et al.* 2009	82 psychosis, FE	VBM technique Tissue type: gray matter	DUI defined as beginning with onset of prodromal symptoms to index admission into the study DUP: onset of psychosis	924/1213	A significant inverse correlation was found between DUI and gray matter density in the left fusiforum gyrus extending into the lingual gyrus and cerebellum. DUI only had major effects in schizophrenia patients, and not in patients with other psychotic disorders
Penttilä *et al.* 2010	46 schizophrenia	MRI scanning. Tissue type: gray matter, white matter, CSF	DUP defined retrospectively based on medical records DUP: the period between the onset of first psychotic symptoms and the beginning of treatment	228/260	DUP did not correlate with the total gray or white matter or CSF volume. DUP associated positively with reduced densities of the right limbic area and the right hippocampus
Malla *et al.* 2011	80 psychosis, FE	VBM technique Tissue type: gray matter, white matter, CSF	DUP: divided into two groups: short DUP ($\leqslant$18 weeks) and long DUP ($\leqslant$18 weeks)	Median: 126	Gray matter volume reduction in the inferior orbital region and parietal area in the long compared to the short DUP group. In addition, there was a significant whole-brain gray matter volume reduction in the longer DUP patients. No differences between the two groups with respect to white matter or CSF volumes

(*b*) *Studies not supporting the neurotoxicity hypothesis*

Study	Subject	Measures	Design and follow-up	DUP (days) Mean/S.D.	Results
Fannon *et al.* 2000	37 schizophrenia, FE	MRI scanning. ROIs: whole brain volume, cortical gray matter, lateral ventricles, temporal lobes	MRI scanning early in the first episode of psychosis in never or minimally treated patients DUP: not defined	197/182	There were no relationships between the duration of psychosis, treated or untreated, and regional brain volumes
Hoff *et al.* 2000	50 schizophrenia, FE	MRI scanning: lateral ventricule, temporal lobe, cerebral hemispheric volume	MRI scannings within 1 month of hospitalization and stabilization on neuroleptics DUP: duration in months of positive symptoms before treatment. DUP also treated as a dichotomous variable, with 1 year as the cut-off point	342/486	No significant correlations were observed between DUP and structural brain deficits at baseline
Malla *et al.* 2002	114 schizophrenia, FE	CT scanning	Association between DUP and various aspects of brain morphology	No information	Evidence of morphological changes: enlargement of sulci and ventricles and a reversed asymmetry of the sylvian fissure. DUP showed no correlation to CT scans
Hietala *et al.* 2003	14 schizophrenia, FE	MRI scans: gray matter in frontal lobe and posterior region	Association between brain volume and DUI	Median: 1080 (range: 150–3600)	No association between DUI and intracranial volume or regional volumes. However, a long DUI predicted reduced gray matter in the left temporal lobe and right posterior region, and an enlarged CSF space in the left temporal lobe
Ho *et al.* 2003	156 schizophrenia, FE	MRI scanning Volumetric measures of: total brain tissue, gray and white matter, CSF Measures of brain surface anatomy	NP assessment and MRI scanning during first episode of psychotic illness, being in the midst of first episode DUP defined as the time period from the onset of full positive syndromes to the initiation of neuroleptic treatment	520/1016	No significant correlations between DUP and brain volumetric measurements or surface anatomy measurements. No significant differences between groups when the group was divided into short and long DUP on the basis of median DUP, except on cortical sulcal depth

FE, First episode; MRI, magnetic resonance imaging; DUI, duration of untreated illness; CT, computed tomography; ROI, region of interest; CSF, cerebrospinal fluid; VBM, voxel-based morphometry; NP, neuropsychological; S.D., standard deviation.

anyway, regardless of whether the person had received treatment or not.

The studies that support the hypothesis have, on average, slightly longer DUP than those who do not (459 *v.* 414 days). This may imply that there is a threshold value for a toxic effect of psychosis (Amminger *et al*. 2002; Gaynor *et al*. 2009), and not a linear relationship between DUP and a neurotoxic effect.

Conclusions

There is limited evidence for a relationship between DUP and changes in neurocognitive functioning or brain structures. Some analyses have shown significant correlations between these variables, but far more studies have shown no such associations. Definite conclusions cannot be drawn because of methodological limitations and a lack of relevant information in existing studies.

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Declaration of Interest

None.

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