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Review

Minimal evidence that untreated psychosis damages brain structures: A systematic review

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ABSTRACT

Introduction: A longer duration of untreated psychosis (DUP) is associated with poor outcomes in first-episode psychosis (FEP); however, it is unclear whether this is due to the effects of psychosis on brain structure. We systematically reviewed the literature on the association between the length of untreated psychosis and brain structure in first-episode psychosis.
Methods: We searched three electronic databases and conducted forward and backward citation searching to identify relevant papers. Studies were included if they: (1) included patients with a psychotic disorder who were treatment naïve or minimally treated; and (2) had correlated measures of DUP or duration of untreated illness (DUI) with structural measures.
Results: We identified 48 studies that met the inclusion criteria. Forty-three examined the correlation between DUP and brain structure, and 19 examined the correlation between DUI and brain structure. There was evidence of significant associations in brain regions considered important in psychosis; however, the proportion of significant associations was low and the findings were inconsistent across studies. The majority of included studies were not primarily designed to examine whether DUP/DUI is correlated with brain structure, and there were methodological limitations in many studies that prevent drawing a strong conclusion.
Conclusion: To date, there is minimal evidence of an association between untreated psychosis and brain structure in FEP. Although the body of literature is substantial, there are few hypothesis-driven studies with a primary objective to answer this question. Future studies should be specifically designed to examine whether untreated psychosis has a deleterious effect on brain structure.

1. Introduction

It is now well established that untreated psychotic symptoms are predictive of clinical and functional outcomes among patients with a first-episode of psychosis. Data from several meta-analyses have shown that a longer period from the onset of psychotic symptoms to the initiation of antipsychotic treatment, known as the duration of untreated psychosis (DUP), is associated with a reduced likelihood of symptomatic remission, a lower level of overall and social functioning, and a poorer quality of life (Marshall et al., 2005; Norman et al., 2005a; Perkins et al., 2005). However, the mechanisms behind this association are currently unknown.

One hypothesis is that the DUP is not a causal factor for poor outcome, but rather a marker for a more severe manifestation of psychotic disorder (McGlashan, 1999). As such, severe cases would develop in a manner that would lead to later detection and initiation of treatment. This is consistent with recent evidence suggesting that people with an insidious onset of schizophrenia had poorer clinical outcomes at both short- and long-term follow-up (Juola et al., 2013). It has also been suggested that the relationship between untreated psychosis and outcome is mediated by social support. An extended period of untreated psychosis has been shown to compromise a person's social resources (Norman et al., 2007), which in turn could have consequences for prognosis (Erickson et al., 1998; Norman et al., 2005b).

An alternative hypothesis put forth by Wyatt in 1991 is that periods of untreated psychosis are 'biologically toxic' to the brain, and this has come to be known as the neurotoxicity hypothesis. This has been postulated to occur via several mechanisms, including glutamatergic

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excitotoxicity (de la Fuente-Sandoval et al., 2011; Natsubori et al., 2014), elevated dopamine levels (Keshavan et al., 1998a; Crespo-Facorro et al., 2007a), persistent catecholaminergic activity (Keshavan et al., 1998a), or prolonged activation of the hypothalamic-pituitary adrenal (HPA) axis (Keshavan et al., 1998a). Indeed, several neuroimaging studies have shown structural abnormalities in brain morphology in the early stages of psychotic disorder (Steen et al., 2006; Chan et al., 2011; Carletti et al., 2012; Fusar-Poli et al., 2012). However, uncertainty remains as to whether active psychotic symptoms exacerbate these structural changes. The neurotoxicity hypothesis has been used to justify involuntary treatment and early intervention efforts as having neuroprotective potential to prevent further degeneration.

The objective of the current study was to conduct a systematic review of the literature on the association between the length of untreated psychosis and various measures of brain structure in patients with first-episode or treatment naïve psychotic disorder.

2. Methods

2.1. Definition of terms

The Duration of Untreated Psychosis (DUP) refers to the period between the onset of the active symptoms of psychosis (delusions, hallucinations, or thought disorder) and the initiation of adequate treatment, including antipsychotic medication and hospitalization. The term Duration of Untreated Illness (DUI) is used to describe the time between the onset of any psychiatric symptoms and the initiation of adequate treatment, such that the DUI includes the putative 'prodromal' period that often precedes the onset of active psychosis (Malla et al., 2002b).

2.2. Search strategy

This systematic review was done in accordance with the guidelines for Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000). We conducted an electronic search of the MEDLINE (1946–2013), EMBASE (1974–2013), and PsycINFO (1967–2013) databases using the OvidSP platform. The MEDLINE search terms are presented in Supplementary Appendix 1, and this strategy was adapted for EMBASE and PsycINFO using analogous terms relevant to those databases. The search strategy was developed in consultation with a medical librarian.

We obtained further studies by manually searching personal files and the bibliographies of relevant studies and review articles. Forward citation searching was done using Web of Knowledge to locate articles that had cited the included studies. When abstracts or unpublished studies were retrieved in our search, we contacted the corresponding authors to determine whether the work had subsequently been published in a peer-reviewed journal. We regularly updated all segments of the literature search, with the final update in December 2013.

One author (KKA) screened the titles and abstracts of all retrieved citations, and obtained the full-text version of relevant articles. Each study was reviewed for the following inclusion criteria: (a) the sample included patients with an affective or non-affective psychotic disorder; (b) the patients were first-episode and either minimally treated or treatment naïve at the time of assessment; (c) brain structure was measured using neuroimaging techniques; and (d) the DUP or the DUI was quantified and correlated with structural measures. We did not impose any restrictions in our search strategy with respect to date, study design, or language of publication. Multiple papers from the same research group with overlapping samples were not excluded provided that different neural structures had been examined. Any circumstances where the inclusion of a study was unclear were discussed among the reviewers (KKA, KM, MR).

2.3. Data extraction and synthesis

Separate data extractions were performed independently for each included paper by two of the three reviewers (KKA, KM, MR). We extracted data on key elements of study design, the definition and measurement of DUP/DUI, and the neural structures examined. All papers were assigned a quality assessment score using a rating scale adapted from the Newcastle-Ottawa Scale (Table 1) (Wells et al., 2013). We adapted this scale for our purposes by adding more specific criteria to the rating options, by adding an additional item for whether or not the exposure (i.e. DUP/DUI) was well defined, and by dividing the section on ascertainment of exposure into the measurement of the exposure and the source of data on the exposure. We removed the items on ascertainment of outcome (i.e. measurement of brain structures) and whether same method of ascertainment was used for the entire sample, as all studies in our review scored the same on these two items. Discrepancies between the reviewers were resolved by consensus. Authors were contacted for further information or clarification when the description of the sample or the definition of untreated psychosis was unclear.

Studies were subdivided based on whether they had measured DUP or DUI according to our definitions, as previously described. When unclear, we contacted the corresponding author to confirm whether DUP or DUI had been measured. We were unable to perform a meta-analysis of the data because there was a substantial amount of heterogeneity in the definition and measurement of the length of untreated psychosis, in the neuroimaging techniques employed, and in the brain structures examined, making the parameter estimates non-comparable across the studies. Additionally, 58% of the DUP studies and 26% of the DUI studies did not report parameter estimates for the association between DUP/DUI and brain structure, but rather commented on whether

Table 1
The scoring system for methodological quality adapted from the Newcastle–Ottawa Scale (Wells et al., 2013).

Legend	Description
Non-participation rate	
+	Low rate and differences described
•	High rate and differences described
−	High rate and/or no description of differences
Definition of the first episode of psychosis (representativeness of participants)	
+	Based on duration of antipsychotic treatment or first presentation to a clinical setting (truly/somewhat representative)
•	Based on first hospitalization (selected group)
−	No description of the derivation of the sample
Adjustment of confounding factors	
+	Adjustment for additional confounding factors* (see below)
•	Adjustment for important confounding factors only (age and/or gender)
−	None
Definition of DUP	
+	Clear definition of DUP
−	Definition of DUP unclear (ex. no description of start/end point)
Measurement of DUP (ascertainment of exposure A)	
+	Use of a standardized measurement tool for dating DUP (structured interview)
−	Not described/Non-systematic method used for dating DUP
Source of data on DUP (Ascertainment of Exposure B)	
+	Patient report corroborated with chart review or third party information (secure record)
•	Patient report only (self-report)
−	Not described/Chart review or third party report only

− Criteria not met; • criteria partially met; + criteria satisfied.
* Potential confounders include medication use, mode of onset, prior substance use, severity, total brain volume.

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