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In Review

The Role of Untreated Psychosis in Neurodegeneration: A Review of Hypothesized Mechanisms of Neurotoxicity in First-Episode Psychosis

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For over 20 years, studies have tried to measure the association between the duration of untreated psychosis (DUP) and changes in brain morphology. A hypothesis that untreated psychosis is neurotoxic has been postulated, but the mechanisms of that toxicity have not been described. We re-analyzed papers collected for a systematic review to extract data on the hypotheses that have been generated on the potential mechanisms by which DUP could impact brain morphology in first-episode psychosis. Dopaminergic hyperactivity, prolonged hypothalamic–pituitary–adrenal activation, and persistent activity of catecholamines have been hypothesized as mechanisms to explain these associations. However, the question remains as to whether the observed structural changes are permanent or may be reversed via antipsychotic treatment.

Le rôle de la psychose non traitée dans la neurodégénérescence : une revue des mécanismes hypothétiques de neurotoxicité dans le premier épisode de psychose

Depuis plus de 20 ans, les études tentent de mesurer l'association entre la durée de la psychose non traitée (DPNT) et les changements de la morphologie du cerveau. Une hypothèse a été émise selon laquelle la psychose non traitée est neurotoxique, mais les mécanismes de cette toxicité n'ont pas été décrits. Nous avons ré-analysé les articles recueillis pour une revue systématique afin d'extraire des données sur les hypothèses générées sur les mécanismes potentiels par lesquels la DPNT pourrait avoir une influence sur la morphologie du cerveau dans un premier épisode de psychose. L'hyperactivité dopaminergique, l'activation hypothalamo-hypophyso-surrénalienne prolongée, et l'activité persistante des catécholamines ont été supposées être des mécanismes pour expliquer ces associations. Cependant, il reste à savoir si les changements structurels observés sont permanents ou s'ils peuvent être inversés par un traitement antipsychotique.

Is there something about being psychotic that is toxic to the individual, beyond the immediate psychotic episode? . . . some patients are left with a damaging residual if a psychosis is allowed to proceed unmitigated. While psychosis is undoubtedly demoralizing and stigmatizing, it may also be biologically toxic.—Wyatt[1, p 347]

In a review published in 1991 examining the effects of neuroleptic drugs on the natural course of schizophrenia, Wyatt[1] noted that early administration of antipsychotic treatment was associated with an improved prognosis among patients with FEP, a finding that has been replicated numerous times.[2–4] Wyatt used the analogy of ischemic heart disease to illustrate his point: repeated ischemic attacks cause cumulative damage that can eventually result in chronic heart failure, and early treatment of ischemic

attacks reduces the damage and scarring to the heart tissue. He argues that prolonged or repeated episodes of psychosis similarly leave scars on the brain, possibly via changes in morphology, biochemical alterations, or damage to neuronal connections.[1] This theory has come to be known as the neurotoxicity hypothesis, and it is one of several mechanisms used to try and explain the observed association between a longer DUP and poor outcomes.[2–4] It has also been used to justify early intervention efforts and involuntary treatment, given their potential for preventing permanent brain damage.

Fast-forward nearly 25 years and we still do not have a clear understanding of the mechanisms behind the observed association between a longer DUP and poor outcomes among patients with FEP. Irrespective of the mechanism, early intervention efforts aimed at symptom detection and comprehensive care during the initial stages of illness are a worthwhile initiative for improving clinical, social, and vocational outcomes,[5–7] as well as for providing cost-effective care.[8–10] However, the question of whether untreated psychosis has a neurotoxic effect on the brain has important ethical and legal implications for the use of coercive and involuntary treatment. Indeed, this question remains very difficult to test empirically, given that confounding factors, such as treatment with antipsychotics,[11–14] cannabis use,[15,16] and other lifestyle habits,[17] have also been found to be associated with changes in brain structure.

There have been 2 recent reviews of the literature specifically investigating the link between DUP and brain structure (Kelly K Anderson, August 22, 2014, personal communication).[18] The conclusions have been equivocal. Many of the included studies did not find evidence to support an association between brain structure and DUP, but the reviews of the literature suggest that the larger studies with the best methodologies are more likely to report positive findings.[18] It has also been suggested that there may be a threshold effect of untreated psychosis, rather than a linear association, such that the neurotoxic effects of psychosis may only be observed at longer lengths of DUP.[18]

There has also been a literature review looking at the association between DUP and neurocognition.[18] Among the 22 studies reviewed, 6 reported associations between cognitive measures and DUP: 2 reported worse general cognitive deterioration with a longer DUP, and the other 4 reported deficits in shifting attention, verbal IQ, visual and verbal memory, and event-based prospective memory. However, 16 studies, in which a total of over 2000 patients were tested with various measures, did not report any association between DUP and neurocognition.[18]

Highlights

- There is some evidence to suggest that the DUP may have a neurotoxic effect on brain structures in FEP.
- Dopaminergic (catecholaminergic) hyperactivity and prolonged HPA activation have been hypothesized as potential mechanisms to explain these associations.
- The question that remains is whether the observed structural changes are permanent or may be reversed via antipsychotic treatment.

In our paper, we will discuss the mechanisms proposed by investigators who have empirically tested the neurotoxicity hypothesis in an effort to explain an association between untreated psychosis and brain structure. To perform our review, we used a database of relevant papers that was produced for a systematic review looking at the association between untreated psychosis and brain morphology (Kelly K Anderson, August 22, 2014, personal communication). The review used MEDLINE, Embase, PsycInfo, and the Web of Knowledge as search engines. It focused on studies that included patients with treatment-naive or minimally treated psychotic disorders in an effort to reduce the confounding effects of antipsychotics and illness chronicity. We looked at studies that measured the DUP, which is the period between the onset of the active symptoms of psychosis (delusions, hallucinations, or thought disorder) and the initiation of adequate antipsychotic treatment.[19] We also looked at studies that had measured the DUI, which is the time between the onset of any psychiatric symptoms and the initiation of adequate antipsychotic treatment, which includes both the prodromal period and the period of active psychosis.[19] The literature review and data extraction methods were based on published guidelines for the conduct of systematic reviews.[20]

Evidence for the association between untreated psychosis and brain structure are presented elsewhere (Kelly K Anderson, August 22, 2014, personal communication).[18] For our review, we identified 9 papers in total where a positive association between the DUP–DUI and brain morphology was found. We then extracted the hypothesized mechanisms proposed in the papers to explain the observed associations. We aimed to get a sample of the thoughts of investigators working in this line of research as to how untreated psychosis may cause damage to brain structures.

Potential Underlying Mechanisms

Among the 9 studies that demonstrated a positive association between DUP–DUI and outcome,[21–29] only 2 of the authors proposed specific biological mechanisms that could potentially underlie structural alterations occurring as a result of the neurotoxic effects of untreated psychosis.[22,24] The authors of both papers proposed a mechanism of dopaminergic hyperactivity,[22,24] whereby the prolonged

Abbreviations

DUI	duration of untreated illness
DUP	duration of untreated psychosis
FEP	first-onset psychosis
HPA	hypothalamic–pituitary–adrenal

elevation of dopamine seen during a psychotic episode leads to a progressive decline in the volume of neural structures, especially in regions with a high concentration of dopamine D_2 receptors, such as the caudate nucleus.[22] Indeed, dopaminergic agents have been shown to induce neuronal apoptosis.[30] The authors cite evidence showing that treatment with antipsychotics is associated with an enlargement in the volume of specific neural structures,[31] and this is believed to occur via blockade of the D_2 receptors.[32,33] Taken together, this evidence begs the question of whether any observed structural changes associated with untreated psychosis reflect neuronal injury, rather than death, that could potentially be reversed with the initiation of antipsychotic treatment.[24]

In a similar vein to the mechanism of dopaminergic hyperactivity, Keshavan et al[24] also propose that neurotoxicity may occur via oxidative injury arising from persistent catecholaminergic activity, as well as from prolonged activation of the HPA axis. In both cases, antipsychotics are proposed to reduce the catecholaminergic activity and HPA activation, respectively, thereby reducing the extent of neuronal damage owing to untreated psychosis.

Alternatively, both Lappin et al[25] and Malla et al[27] raise the possibility that the observed structural abnormalities may be a marker for poor premorbid functioning or an insidious onset of psychotic disorder, consequently leading to a longer delay in detection and initiation of antipsychotic treatment. Indeed, there is evidence to suggest that people who have poor levels of premorbid functioning, especially during childhood, are more likely to show computerized tomography scan abnormalities.[34] Although other studies have shown an association between poor premorbid functioning and the length of the DUP,[35] Malla et al[27] did not find a difference in premorbid adjustment between patients with a longer and shorter DUP, suggesting that this hypothesis could not explain grey matter deficits observed in the longer DUP group in their study.

Limited Evidence to Support the Neurotoxicity Hypothesis

We present the hypotheses from 9 studies that have shown a link between untreated psychosis and brain morphology.[21–29] However, note that there are many additional studies that have not found evidence of an association between DUP–DUI and structural abnormalities in FEP (Kelly K Anderson, August 22, 2014, personal communication).[18] The common criticisms of these negative studies is that they have small sample sizes and that they include patients who have already been exposed to antipsychotics. Additionally, most studies that investigate the validity of the neurotoxicity hypothesis using measures of neurocognitive functioning do not find an association with DUP.[18]

McGlashan[36] outlines several reasons why active psychosis is unlikely to have a biologically toxic effect, specifically:

1) the effect of DUP on outcome plateaus at longer lengths of treatment delay,
2) neuronal degeneration is evident prior to the onset of the active symptoms of psychosis,
3) there is no evidence to suggest that functional deterioration is cumulative with each relapse, and
4) a lack of evidence of neuronal death observed in post-mortem brains of people with schizophrenia.

Limitations of the Literature to Date

The challenge with the discussion on potential mechanisms of neurotoxicity may, in part, reflect general issues with the literature, to date, on the association between untreated psychosis and brain structure. Many studies have empirically examined this association, but there have been many methodological problems with this body of literature. Any rigorous investigation of the neurotoxicity hypothesis faces many complex methodological questions: Which brain structures should be considered? What types of neuroimaging techniques should be used? Does this imaging technique accurately measure the functional changes that are seen in psychosis? Are there structural changes occurring at a microscopic level that current imaging approaches may not be able to detect in vivo? Should samples include people with psychosis generally, or people with schizophrenia specifically, given how difficult it is to make diagnoses at the first episode? How can we account for the myriad confounding factors?

In addition to these challenges, the fundamental issue that has plagued all studies in the field of early psychosis is the measurement of the DUP.[37] It may be that the measurement of DUP is a significant impairment to identifying and describing any morphological changes that are linked to it, let alone describing credible hypotheses to explain mechanisms of biological toxicity. Limitations in our understanding of the natural history of the illness and to our ability to accurately identify people with FEP may make it difficult not only to accurately measure DUP but also to describe its mechanisms.

As previously described, the DUP is the period between the onset of the active symptoms of psychosis (delusions, hallucinations, or thought disorder) and the initiation of adequate antipsychotic treatment.[19] Although it appears to be straightforward at first glance, DUP has proven to be a difficult construct to define, measure, and operationalize,[37] and there is often a great deal of inconsistency across studies. This is because of the variability in the onset of schizophrenia, and because a decision has to be made as to when treatment has started.

Regarding the onset of active psychosis, some people with schizophrenia have a difficult-to-define onset that begins many years previously without clear psychotic symptoms, whereas others have good preservation of personality and functioning followed by an acute onset. Morphological changes in the brain may be associated with the type of onset, such that people with an insidious onset may be more likely to show structural abnormalities. Measuring the start date for patients with acute-onset psychosis is much easier than for those with an insidious onset. This may lead to an

underestimate of the length of the DUP in patients with insidious-onset psychosis, thereby decreasing our ability to measure the link between DUP and morphological changes in the brain. However, even if it were possible to accurately measure the date of onset of psychosis in the insidious group, it may be that this does not measure the onset of illness, and consequently does not measure the start of morphological changes in the brain. One approach to dealing with this issue has been to measure the DUI rather than the DUP, which attempts to measure when psychiatric problems actually start. The difficulty that arises with this approach is that, retrospectively, there are numerous symptoms that may or may not be truly prodromal, and because of this we introduce measurement error. A further problem is that prodromal symptoms may be linked to factors that increase the risk of psychosis rather than the disease process itself, and untangling this may be just as problematic.

Similar to the issues of dating the onset of the illness, there are issues about deciding when the illness is first treated. Generally, the end point of DUP–DUI is the initiation of adequate antipsychotic treatment. However, there is currently no hard-and-fast rule as to what constitutes adequate antipsychotic treatment, but the standard definition is typically treatment with an antipsychotic for a period of 1 month. Ignoring the problems with knowing whether someone has actually taken the drug for a month, it is unclear whether initiating treatment ceases brain changes, or which treatments may have an impact. There have been arguments that just as there are many different facets to psychosis, there are similarly many different treatments, such as cognitive-behavioural therapy, which have been shown to have some benefit, as well as social interventions, such as work and housing, which have an important impact on prognosis. Therefore, if we are actually going to use the initiation of adequate treatment as a meaningful end point, it may need to have a broader conceptualization.

Conclusions

There is some evidence to suggest that the DUP may have a neurotoxic effect on brain structures in FEP. Given the current limitations of the literature, many researchers have been prudent in what seems a reluctance to speculate on which mechanisms may be involved in the neurotoxicity of untreated psychosis. Dopaminergic (catecholaminergic) hyperactivity and prolonged HPA activation have been hypothesized as potential mechanisms to explain these associations, and the question remains as to whether the observed structural changes are permanent or may be reversed via antipsychotic treatment.

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