

## Editorial

# A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic)

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## Summary

Schizophrenia is usually classified based on clinical presentation. However, the conventional paranoid–disorganised–residual distinctions have had limited clinical utility. Here we draw on the evidence for differences in pathophysiology underlying treatment response to propose a subclassification based on neurobiology to guide diagnostic testing and treatment.

## Declaration of interest

In the past 3 years O.H. has received investigator-led grants and/or served as a speaker/consultant for Eli Lilly, Roche, Leyden-Delta, Lundbeck, Servier and Janssen-Cilag (J&J). S.K. has received grant support from GlaxoSmithKline, GW and Roche and has served as a one-off consultant and/or speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Envivo, Janssen (J&J), Otsuka, Pfizer and Takeda, and serves on scientific advisory boards for Lundbeck and Roche.

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## Diagnostic classification and schizophrenia

Diagnostic classification serves a number of medical and social purposes but perhaps the most clinically important is as a guide to treatment. Thus, the distinction between diabetes mellitus and diabetes insipidus has profound implications for treatment – insulin is highly effective for the former but not for the latter, whereas the reverse is true for anti-diuretic hormone. This distinction arose because of careful clinical observation coupled with advances in biology which established that what was considered one syndrome (diabetes) was in fact two distinct disorders, each with a completely different pathophysiology.

Traditionally our diagnostic systems divide schizophrenia into a number of subtypes (five in DSM-IV<sup>1</sup> and eight in ICD-10<sup>2</sup>) based on clinical features. Despite being present for over three decades in various forms, subtypes of schizophrenia have been, or are set to be, removed from the latest revisions of our diagnostic systems (DSM-5 and ICD-11), due to their lack of reliability, prognostic validity and implications for treatment (<http://www.dsm5.org/Documents/changes%20from%20dsm-iv-tr%20to%20dsm-5.pdf>). Instead, clinicians will be able to use dimensional assessments based on key symptom domains covering positive, negative, affective and cognitive symptoms. The patient will thus receive a diagnosis of schizophrenia and an indication of the severity of symptoms across each dimension. Implicit in these changes is a view of that there is 'one schizophrenia', albeit with heterogeneity.

The DSM and ICD classifications ignore the one subtyping of schizophrenia that is almost universally accepted clinically – the distinction into treatment-refractory and treatment-responsive illness. The clinical value of this categorisation is clear – it is

enshrined in clinical guidelines around the world and one drug, clozapine, is licensed as the only treatment for refractory schizophrenia. As a formal diagnostic category it is limited because it requires a series of empirical trials of different antipsychotic drugs. Nevertheless, this distinction is useful if it points to fundamental differences in the pathophysiology underlying treatment-responsive and treatment-refractory schizophrenia.

## Dopamine, schizophrenia and the action of antipsychotic drugs

The initial evidence linking dopamine dysfunction to schizophrenia was indirect, derived, for example, from observations that drugs such as amphetamine that increase dopamine levels worsen psychotic symptoms, and that drugs such as reserpine that deplete dopamine levels, reduce psychotic symptoms.<sup>3</sup> Further support came from findings of increased dopamine metabolite levels in the cerebral spinal fluid and plasma of patients with schizophrenia.<sup>3</sup> These studies could not localise the dopamine dysfunction to the brain, but subsequent post-mortem and molecular imaging studies provided evidence for abnormalities specifically in brain dopaminergic function. There have now been over 50 *in vivo* molecular imaging studies of dopamine function in over 1000 patients.<sup>3</sup> This provides robust evidence for presynaptic dopamine dysfunction in schizophrenia – with a large (0.8) effect size – and studies in patients with prodromal schizophrenia have linked this to the onset of the disorder.<sup>4</sup>

In the 1970s it was found that the potency of antipsychotic drugs at dopamine D<sub>2</sub> receptors was closely correlated with the clinically effective dose. This was followed by molecular imaging studies of antipsychotics showing that substantial dopamine receptor blockade is seen with clinically effective doses and is needed for treatment response. Furthermore, meta-analysis indicates that very selective dopamine-blocking drugs such as amisulpride are as effective as or, in some cases, more effective than drugs that act at multiple receptors. There is thus converging evidence to indicate that dopamine blockade is central to treatment response, and may be sufficient in some instances.

## Dopamine and treatment response

The studies discussed above have tended to treat schizophrenia as one entity. However, it has been clear right from the introduction of chlorpromazine that not all patients respond to antipsychotics, and this was later confirmed in careful clinical studies. Positron emission tomography (PET) imaging has shown that some patients show little or no response even with high levels of dopamine receptor blockade (reviewed in Demjaha *et al*<sup>5</sup>), and patients with treatment-refractory illness show no benefit from treatment that depletes dopamine levels.<sup>6</sup> Thus, although dampening dopamine neurotransmission works for many patients, it is not sufficient for response in others. This suggests that there are dopaminergic differences between patients.

Several lines of evidence indicate that there are differences in the dopamine system between patients who respond to antipsychotic drugs and those who do not. First, there is evidence from studies that have investigated dopamine metabolite levels in drug-free patients with schizophrenia. These show a bimodal distribution, suggesting that there is a group with high dopamine activity and another group with unaltered dopamine activity.<sup>7</sup> Higher baseline dopamine metabolite levels are generally associated with good subsequent response to antipsychotic treatment, whereas lower dopamine metabolite levels are associated with poor response.<sup>8</sup> Second, post-mortem brain dopamine levels were found to be higher in the striata of patients who had responded to treatment than levels in those who had not responded.<sup>9</sup> Finally, there is the evidence from molecular imaging studies, that, although there is a consistent alteration in dopaminergic function in schizophrenia, there is also evidence of heterogeneity.<sup>3</sup> As these studies have not distinguished between responders and patients with refractory illness, the inclusion of the latter is one potential explanation for the heterogeneity. Interestingly, it has long been recognised that, in contrast to the majority of patients with schizophrenia, amphetamine does not induce psychotic symptoms in some patients, and imaging studies show that some patients show unaltered dopamine release to amphetamine (see Howes *et al*<sup>3</sup>). Further evidence comes from a study that looked at the relationship between synaptic dopamine levels and subsequent treatment response.<sup>10</sup> This found that patients with the highest synaptic dopamine levels showed the best response to subsequent antipsychotic treatment, although whether the poor responders had treatment-refractory schizophrenia was not investigated. Finally, a study specifically comparing dopamine function in treatment-refractory and treatment-responsive schizophrenia found that dopamine synthesis capacity was elevated in patients with treatment-responsive compared with treatment-refractory illness, with a very large effect size – over 1.1.<sup>5</sup> Interestingly, patients with treatment-refractory schizophrenia showed no alteration in dopamine synthesis capacity compared with healthy volunteers.

## Subtypes of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic)

The evidence reviewed above links dopaminergic alterations to the onset of psychosis in the majority of patients with schizophrenia but also highlights emerging evidence that this is not the case in all patients. Based on this we propose two subtypes of schizophrenia: type A (hyperdopaminergic) characterised by elevated striatal dopamine synthesis and release capacity, and type B (normodopaminergic) where these dopaminergic alterations are not present. In the case of type A schizophrenia, hyperdopaminergia underlies the onset of the disorder, increasing as the illness

first develops and leading to the development of symptoms. Understandably, this type shows a good response to the dopamine-blocking antipsychotics. In contrast, type B is theorised to show normal dopaminergic function and symptoms that are unrelated to dopaminergic function.

The proposed subtyping has several potential advantages over the current phenomenological classification or the move to dimensions. First, it is based on a neurobiological mechanism with implications for treatment choice – and thus can unite academic classification and clinical utility. Second, it has clear implications for treatment: type A (hyperdopaminergic) schizophrenia will respond to dopamine-blocking drugs, whereas type B, where there is no elevation in dopamine, will not. Third, by focusing on mechanisms over phenomenology it provides a sound basis for research that has the potential to lead to new treatment options. For example, research into type B could potentially identify new targets that would be effective for patients whose illness responds poorly to current antipsychotics, offering better-tolerated alternatives to clozapine, the only drug currently licensed for this indication. Fourth, it could lead to tests that guide treatment choice at illness onset – this could enable type B patients, who we predict will not respond to conventional antipsychotics, to be fast-tracked to clozapine or new treatments as they emerge. In this respect, PET imaging of dopamine in schizophrenia has already been shown to have high sensitivity (89%) and specificity (94%).<sup>11</sup> This has the potential to greatly improve treatment, given the current long delays and costs associated with refractory schizophrenia.<sup>12</sup> Finally, it is a hypothesis that can be tested and refuted; for example, by showing that patients with type B show a dopaminergic abnormality or that hyperdopaminergia does not lead to psychosis in type A patients.

Of course, our subtyping begs the question: what underlies type B schizophrenia? Several likely candidates exist, with glutamatergic alterations probably foremost. But it would be premature to specify one over the other at this stage, although we expect normodopaminergic to be replaced with one of these candidates in the fullness of time. Ultimately, this or any other subtyping will stand or fall on its clinical utility. Nevertheless, given the singular lack of clinical impact of phenomenologically based classifications over the past three decades, we will do our patients a disservice if we continue to be satisfied with descriptive typing of schizophrenia, whether by dimensions or categories, unless it is anchored to biology.

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First received 11 Sep 2013, final revision 25 Sep 2013, accepted 1 May 2014

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## psychiatry in pictures

### Stages of Mental Illness

Lesley Harper



In this painting I tried to make sense of my illness. The shapes represent my personality, they disintegrate from left to right with the passage of time. The background colours stand for changes I went through, i.e. the white blast represents the death of my Dad when I was 16.

This painting is 6 foot long and if it continued, the shapes would reassemble into some kind of order. I have hope for the future.

My episodes of psychosis have occurred less often as I get older. I work as a self-employed artist which allows me to work at my own pace. It is very therapeutic. I have insight into my condition and know when to ask for help. Although I cannot prevent schizophrenia, I have learned to live with it.

The British Journal of Psychiatry (2014)  
205, 3. doi: 10.1192/bjp.bp.113.140178