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"Understanding and predicting variability in response to treatment in psychotic disorders:

in vivo findings"

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Introduction

Psychotic illnesses such as schizophrenia and bipolar affective disorder are severe mental disorders characterised by delusions and hallucinations. They have a lifetime prevalence of approximately 3%, and are associated with decreased life expectancy of 15-20 years compared to the general population; highlighting the importance of patients receiving effective treatment.

The main treatment for psychosis is antipsychotic medication, both for acute psychotic episodes and relapse prevention. These drugs are effective; showing an average pooled effect size for psychotic symptom reduction of around 0.5 for acute episodes. However, this belies striking variability in response between individuals: some patients show dramatic improvement, whilst others show little or no change in symptoms.

The last decade has seen the field increasingly recognize symptom reduction on a rating scale may not translate into meaningful clinical improvements. Studies indicate that a decrease of at least 30% in psychotic symptom severity is the minimum clinically meaningful change. Unfortunately, about 1 in 3 patients do not experience clinically meaningful response to first-line antipsychotics, termed treatment resistance. Treatment resistance is seen in around 15-20% of people with schizophrenia from illness onset; and develops over time in a further 15% whose illness initially responded to antipsychotic treatment.

There is currently only one drug licensed in treatment resistant schizophrenia, clozapine. Whilst clozapine leads to symptomatic and functional improvements, and reduced mortality, use is limited by risk of potentially life-threatening side-effects. Therefore, it is important to ensure psychosis is unlikely to respond to other drugs before introducing

clozapine. Recognition of this has led to a focus on understanding causes of variability in treatment response, and developing biomarkers to guide treatment choice.

Pseudo-treatment resistance

In clinical practice some people are given diagnoses of treatment resistant illness when other factors account for lack of response, “pseudo-treatment resistance.” These include poor oral antipsychotic concordance, or pharmacokinetic effects, such as poor absorption or rapid metabolism. Therefore, determining treatment-resistance first requires ensuring adequate concordance, by combining measures such as self-report, family report with objective measures such as antipsychotic levels and use of long-acting injections. However, the optimum measure is showing the drug has reached its target site in the brain at adequate levels. Neuroimaging is the best in vivo approach for this.

The role of neuroimaging in understanding variability in response

The initial focus of neuroimaging in psychosis was brain structure. Early CT and MRI imaging findings showed larger ventricular volume, thought to be secondary to lower levels of grey and white matter, was associated with poorer clinical response. In addition, diffusion Tensor Imaging (DTI) studies have shown reduced white matter integrity in non-responders compared to responders. Generally, structural alterations in non-responders are more marked rather than categorically different to brain structure in responders (1).

Functional Magnetic resonance imaging (fMRI) has also examined response. Resting-state fMRI analyses show baseline cortico-striatal functional connectivity associated with subsequent antipsychotic response with 80% sensitivity and 75% specificity. Thus, both

functional and structural MR can determine brain changes linked to variation in antipsychotic response. However, as mechanism by which these differences might underlie response is unclear, we will focus on neurochemical imaging that indexes neurotransmitter systems relevant to antipsychotic action.

What has imaging told us about the biological basis for psychosis?

Hyperactivity of the subcortical dopamine system is widely thought to underlie the development of psychosis, at least in most patients. Involvement of dopamine in the pathoetiology of psychosis was initially based on observations that amphetamine congeners induce psychosis in healthy people and worsen psychosis in psychotic disorders. However, it was not until development of single photon computed tomography (SPECT) and positron emission tomography (PET) that it was possible to show this was linked to dopamine release. Meta-analysis of studies of striatal $D_{2/3}$ receptor density and dopamine transporter alterations in schizophrenia show these systems to be unlikely to be altered; In contrast, studies show marked elevations in dopamine synthesis capacity and dopamine release to amphetamine in schizophrenia, including in antipsychotic free/naïve patients (2). Greater dopamine release following amphetamine was directly associated with greater induction of psychotic symptoms, indicating dopamine release can induce psychosis. Furthermore, in people at high risk of psychosis, there appears to be elevated dopamine synthesis capacity in people who develop psychosis, compared to those who do not. Synthesis of this literature (incorporating over 40 molecular imaging studies) found an overall large effect size (Cohen's $d=0.8$) elevation in striatal dopamine release and synthesis capacity in schizophrenia compared to controls. Thus, excess dopamine synthesis and release seem to drive the development and relapse of psychosis.

Imaging evidence on how antipsychotic drugs work: receptor occupancy and clinical response

All currently licensed antipsychotics block dopamine $D_{2/3}$ receptors in-vitro but it was unclear whether this was important for their clinical action. SPECT and PET have shown in-vivo that antipsychotics cross blood-brain barrier, and at clinically effective doses occupy a substantial proportion of striatal $D_{2/3}$ receptors in healthy people and patients. Meta-analysis of imaging studies in patients shows antipsychotic $D_{2/3}$ occupancy by antipsychotics explains about 25% of clinical response, with the potential exceptions of clozapine and quetiapine. The relationship has also been tested prospectively, Kapur et al examining the effects of low and moderate dose haloperidol on $D_{2/3}$ receptors in first episode schizophrenia. They found striatal $D_{2/3}$ occupancy by haloperidol separated responders from non-responders: those with occupancy greater than about 65% were more likely to respond to antipsychotic treatment (3). Occupancy at serotonin 2A and 1A receptors have also been suggested as potentially contributing therapeutic action of some antipsychotics. However, imaging studies have not found clear links between occupancy at these receptors and variability in response.

In summary, antipsychotics act to block $D_{2/3}$ receptors to dampen consequences of excess dopaminergic neurotransmission, explaining about 25% of variability in response. This raises the question of whether they normalise underlying dopaminergic dysfunction. Recent evidence suggests they do not, at least at standard therapeutic doses (4). It also raises the questions of what accounts for the remaining variability in response.

Imaging findings on dopaminergic function in treatment non-responders

Whilst it is clear that levels of $D_{2/3}$ occupancy can explain variability in response to most antipsychotics, a key question is whether high occupancy guarantees response. PET and SPECT studies showed, despite high $D_{2/3}$ occupancy, a proportion of patients did not significantly respond to treatment; indicating that whilst $D_{2/3}$ occupancy may be necessary for response, it does not guarantee it. Molecular imaging studies therefore examined the relationship between the presynaptic dopamine system and antipsychotic response to determine if differences in underlying dopaminergic dysfunction accounted for this variability. An initial SPECT study used a technique that provides an index of synaptic dopamine levels, finding striatal synaptic dopamine positively correlated with subsequent antipsychotic response, explaining about 34% of variability in psychotic symptom response. Further examination of the presynaptic system in treatment resistant schizophrenia found lower striatal dopamine synthesis capacity in treatment resistant illness compared to those with schizophrenia whose illness had responded to antipsychotics. This was also found in people with treatment resistant illness taking clozapine relative to patients whose symptoms responded to first-line antipsychotics. These cross-sectional findings have recently been extended in a prospective [^{18}F] -DOPA study in people with first episode psychosis, which avoids potential confounds of illness duration and antipsychotic use that could have affected prior studies. This found around 40% of response in positive psychotic symptoms was explained by initial dopamine synthesis capacity (5). Thus, imaging of presynaptic striatal dopaminergic function explains a moderate-large degree of variability in response to antipsychotics.

Imaging findings of glutamatergic function in non-responders

The findings discussed above suggest a non-dopaminergic abnormality may underlie treatment resistance, raising the question of what underlies psychosis in these patients? The field has focused on other neurotransmitter systems, specifically the excitatory neurotransmitter glutamate, measured using magnetic resonance spectroscopy (MRS). The MRS literature has suggested elevation in anterior cingulate glutamate (specifically the glutamate/creatine ratio) as a marker of poor treatment response, in three different cohorts, in antipsychotic naïve/minimally-treated first episode schizophrenia, and cohorts with established schizophrenia. The degree of variability explained is less than the dopaminergic findings above: analysis of antipsychotic naïve participants indicates that about 13% of variance in change in total psychotic symptoms (PANSS) was explained by Glu/Cr ratio in the anterior cingulate cortex.

Conclusions and future directions

In vivo imaging studies show presynaptic dopamine function explains at least a third, and D2/3 receptor occupancy about 25%, of variability in response of psychotic symptoms to treatment. It remains unknown how much variability they would explain if combined but if, as discussed above, treatment resistance is a non-dopaminergic form of psychosis then this may not be much more than measured separately. What then explains the remaining variability? A proportion of response is related to non-drug effects, reflected in placebo response, and therefore it is unlikely these measures will explain all variability in response. Notwithstanding this, MRS, functional and structural imaging findings indicate interactions with other systems are likely to explain additional variance. This warrants testing in studies that combine measures. Studies also need to test sensitivity and specificity of measures to identify treatment resistant patients in real world settings, to determine translational

potential. Finally, we have focussed on psychosis in schizophrenia where most of the evidence lies. However, recent findings suggest the same principles may also apply to response in bipolar disorder, which requires further testing.

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Conflicts of interest

Professor Howes has received investigator-initiated research funding from and/or participated in advisory/ speaker meetings organized by Astra-Zeneca, Autifony, BMS, Eli Lilly, Heptares, Janssen, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. Neither Professor Howes nor his family have been employed by or have holdings/a financial stake in any biomedical company.

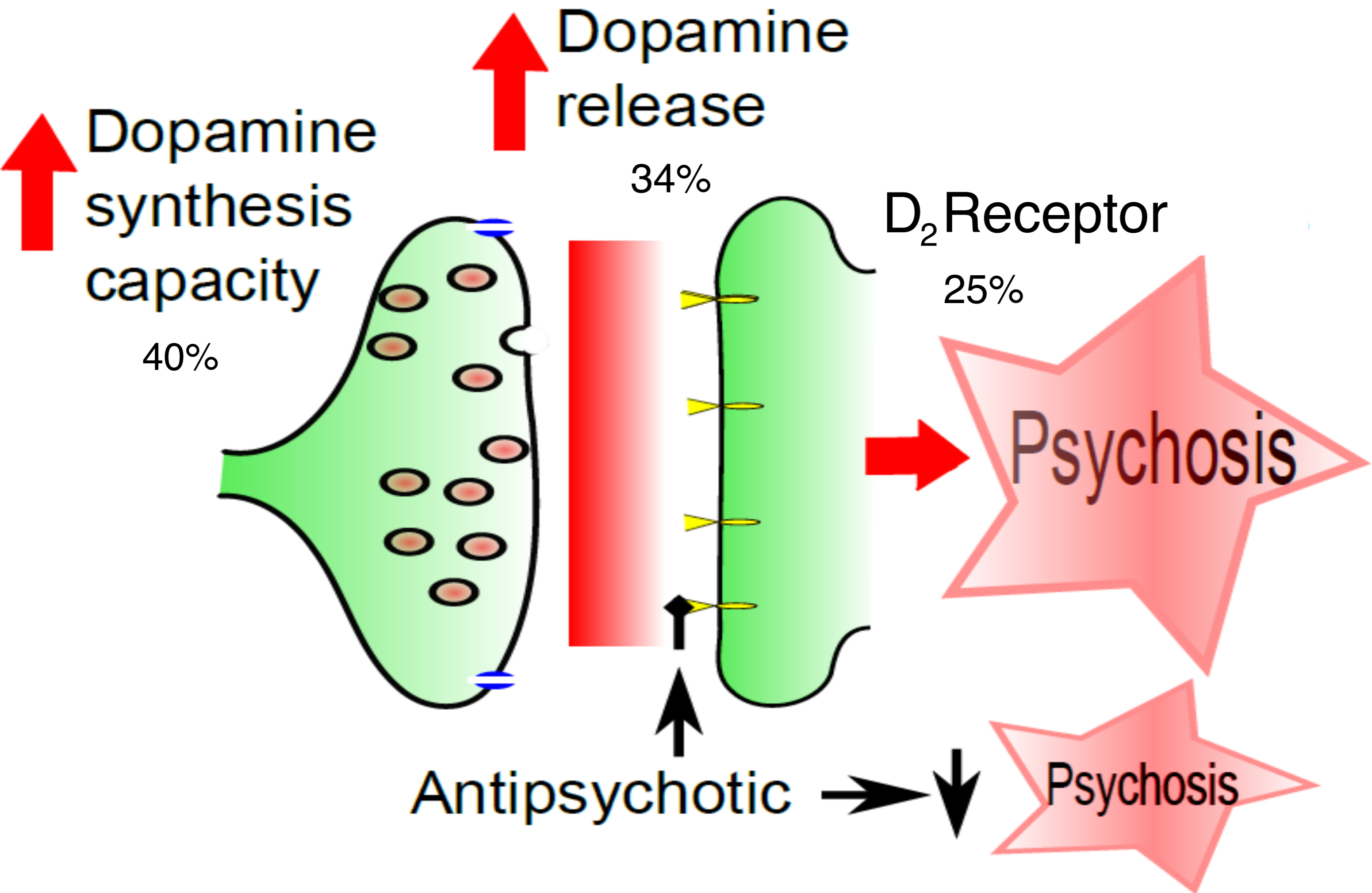
Dr Jauhar reports no conflict of interest.

Author contributions; both authors contributed equally to the writing of this manuscript.

Figure legend; Figure indicating the aetiological role of dopamine in psychosis and action of antipsychotic drugs on the dopamine system, with variability of response indicated for different parts of the dopamine system.

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Dopamine synthesis capacity

40%

Dopamine release

34%

D₂ Receptor

25%

Psychosis

Antipsychotic

Psychosis