Epidemiology and Psychiatric Sciences (2014), **23**, 333–336. © Cambridge University Press 2014
doi:10.1017/S204579601400064X

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Paolo Brambilla, *Section Editor*

Basal ganglia anatomy and schizophrenia: the role of antipsychotic treatment

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Progressive enlargement of basal ganglia volume has been observed in schizophrenia individuals, potentially being sustained by chronic administration of antipsychotic drugs. Here we briefly summarise the state of the art of the role of antipsychotic in leading to increased basal ganglia in schizophrenia, particularly focusing on the caudate nucleus.

Received 19 August 2014; Revised 15 September 2014; Accepted 15 September 2014

Key words: Caudate, globus pallidus, schizophrenia, sMRI, striatum.

It has consistently been shown that schizophrenia is associated with progressive and widespread structural brain changes, mainly including prefrontal cortex, basal ganglia and limbic regions. However, whether these brain abnormalities are static or change over time remains controversial (Roiz-Santiáñez *et al.* 2013). In this context, antipsychotic treatment needs to be taken into consideration, particularly for basal ganglia, which highly express dopamine D2 receptors. Indeed, the dopaminergic hypothesis of schizophrenia argued that the hyperactivity of the dopamine system is responsible for illness' symptoms, particularly positive symptoms. In this regard, dosage-dependant increased basal ganglia volumes have been shown in patients with chronic schizophrenia treated with antipsychotics (see Supplementary Table 1). Therefore the role of antipsychotic medication in altering basal ganglia morphology in schizophrenia cannot be underestimated. In particular, caudate represent the major target area for the subcortical dopamine projections involved in movement control, learning and memory. Interestingly, enlarged caudate has been shown in patients treated with first generation antipsychotic but not in those on second generation (Oertel-Knöchel *et al.* 2012). Also, despite some investigations had reported smaller caudate nucleus volumes in first episode patients compared with healthy subjects (Keshavan *et al.* 1998), several others found preserved caudate size in never or minimally medicated patients (Lang *et al.* 2001; Tauscher-Wisniewski *et al.*

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2002; Crespo-Facorro *et al.* 2007). Therefore caudate changes might occur early in the course of treatment in young first-episode patients as an interaction between antipsychotics and the plasticity of dopaminergic neuronal systems (Chakos *et al.* 1994).

The chronic blockade of D2 receptors induced by antipsychotics would stimulate the proliferation of D2 receptors, resulting to an increase in neuronal size or dendritic tree ultimately leading to increased caudate size. This is more evident in chronic treated patients with first generation antipsychotics, such as haloperidol, which have higher D2 antagonistic effects which ultimately induce extrapyramidal symptoms. In contrast, the second generation agents seem to preserve such enlargement (Scheepers *et al.* 2001). For instance, clozapine exerts its antagonistic effect predominantly through the blockade of D3 and D4 receptors, which are weakly expressed in basal ganglia. Nonetheless, some studies showed that greater caudate volumes before the start of antipsychotic treatment associated with greater symptoms' improvements (Hutcheson *et al.* 2014). These findings suggest that, to some extent, basal ganglia size is a candidate biomarker to evaluate the effectiveness of antipsychotic response, particularly in attenuating positive symptoms. In this regard, it has been shown that siblings and offspring of subjects with schizophrenia have intermediate striatal volumes between controls and patients, potentially representing a sign of risk for the disease (Perez-Costas *et al.* 2010).

In conclusion, the increase of basal ganglia volumes in patients with schizophrenia appears to be related to the D2 blockage due to antipsychotic administration, which is particularly relevant for first generation agents and chronic administration. Also, there is some evidence that gross striatal morphological changes may represent candidate marker for the risk and outcome of the illness. Considering that something between 20 and 30% of patients with schizophrenia are poorly responders, the detection of neural underpinnings of antipsychotic response would greatly improve treatment efficacy and eventually patients' quality of life. Future larger and longitudinal studies investigating basal ganglia volumes before and after selective first and second generation agents in medication-naïve patients are expected to further and better evaluate the potential role of striatum as a biomarker of prediction of antipsychotic response in schizophrenia.

Acknowledgements

P.B. was partially supported by grants from the Italian Ministry of Health (grant no. GR-2010-2316745).

Financial support

The authors received no specific grant from any funding agency, commercial or not-for-profit sectors for this publication.

Conflict of Interest

None.

Supplementary Materials

The supplementary materials referred to in this article can be found at http://dx.doi.org/10.1017/S204579601400064X

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https://doi.org/10.1017/S204579601400064X Published online by Cambridge University Press