Sarro et al report that in patients with schizophrenia, tardive dyskinesia is associated with widespread deficits in the amount of cerebral grey matter, most prominently in the basal ganglia and thalamus, but also in frontal and temporal cortex. The word 'tardive', denoting delayed onset following initiation of antipsychotic treatment, implies that antipsychotic medication plays a substantial causal role in tardive dyskinesia. However, recurring dyskinetic movements of facial and limb muscles, indistinguishable in form from tardive dyskinesia, are observed in patients with schizophrenia who have never been exposed to antipsychotics. Therefore, understanding the pathophysiology of dyskinesia in schizophrenia assumes special clinical importance. Evidence of association observed in cross-sectional imaging studies cannot prove cause, but relevant experimental investigations would be unethical and impractical in humans. This means that we must endeavour to draw what conclusions we can from the associations revealed by cross-sectional imaging studies.

Because brain imaging has been employed more extensively in the investigation of other symptoms of schizophrenia, it is instructive to compare what imaging has revealed about dyskinesia with what has been learned about auditory hallucinations. Like dyskinesia, hallucinations are transient phenomena typically lasting a matter of seconds, but nonetheless usually recurring on multiple occasions in schizophrenia. This time course implies that symptom manifestation is likely to reflect transient aberrant neurotransmission in the relevant brain circuit occurring against a background of a persistent predisposing factor. Dopamine blockade with antipsychotics can suppress both dyskinesia and superior temporal gyrus in the case of auditory hallucinations. It is noteworthy that in the case of dyskinesia, the implicated region of the basal ganglia is the caudate nucleus rather than putamen. Although the putamen is engaged in execution of simple motor actions, the caudate is part of a circuit including dorsomedial thalamus and frontal cortex that is engaged in executive control of motor actions. Similarly, in the case of auditory hallucinations, the implicated regions include not only auditory processing regions in superior temporal gyrus, but also the insula which plays a key role in the allocation of attention to stimuli according to their behavioural salience.

Contrary to this, there is compelling evidence that a pathological process affecting microstructural elements of brain cells leads to subtle deficits in the amount of grey matter. In most cases the amount of grey matter lies within the normal range, and the deficit is only discernible by examining group averages. The nature of the microstructural abnormality remains uncertain, but much evidence is consistent with a disorder of synaptic structure that affects the amount of grey matter. In most cases the amount of grey matter is only assessed using cross-sectional imaging in healthy controls. Despite extensive investigation, many details of the pathophysiology of schizophrenia remain uncertain. Nonetheless, there is compelling evidence that a pathological process affecting microstructural elements of brain cells leads to subtle deficits in the amount of grey matter. In most cases the amount of grey matter lies within the normal range, and the deficit is only discernible by examining group averages. The nature of the microstructural abnormality remains uncertain, but much evidence is consistent with a disorder of synaptic structure that affects the amount of grey matter. In most cases the amount of grey matter is only assessed using cross-sectional imaging in healthy controls.
Perhaps the most parsimonious interpretation of the evidence is that the major predisposing factor underlying all the symptoms characteristic of schizophrenia, including hallucinations and dyskinesia, is a similar microstructural abnormality that affects communication between brain regions, with the form of symptoms being determined by which brain regions are involved. However, before concluding that it is likely that a similar microstructural pathology contributes to hallucinations and dyskinesia, it is important to consider respects in which hallucinations and dyskinesia differ.

### Other predisposing factors

First, the two types of symptoms differ in age dependence. The prevalence of orofacial dyskinesia in schizophrenia increases markedly with age, suggesting that age-related degeneration plays a significant role in many cases. Of relevance to the relationship between the pathophysiology of schizophrenia and dyskinesia, patients with more severe negative symptoms tend to have onset of dyskinesia at a younger age. However, even in cases with substantial negative symptoms, the mean age at onset is in the mid-40s, whereas onset of the florid psychotic symptoms of schizophrenia, including hallucinations, typically occurs two decades earlier. Although the occurrence of hallucinations in dementia suggests that age-related degeneration can contribute to hallucinations, the association with aging is much stronger in the case of dyskinesia. Age-related degeneration might account for the observed tardy onset of dyskinesia.

Isolated hallucinations and dyskinesia can both occur in otherwise healthy individuals, but the predisposing factors tend to differ. For example, whereas age increases the likelihood of dyskinesia, sleep deprivation is associated with hallucinations. Despite the pharmacological similarities, such as acute suppression of both hallucinations and dyskinesia by dopamine blockers, there are differences. There is relatively little overlap between drugs considered to be hallucinogenic and those that are reported to cause dyskinesia. Most important is the observation from naturalistic clinical studies that treatment with a higher dose of antipsychotics is associated with a greater risk of dyskinesia, although the likelihood that more severe cases are prescribed higher doses should be borne in mind. Cautious reduction in dose is often recommended for the management of tardive dyskinesia, although there is little evidence to support this recommendation. Despite the lack of evidence from appropriately controlled studies, a substantial body of evidence from observation of routine clinical practice does suggest that antipsychotic drugs play a causal role in tardive dyskinesia. Overall, the evidence indicates that it would be far too simplistic to conclude that the difference in the pathophysiology of hallucinations and of dyskinesia is merely a matter of differences in the brain regions affected by the pathologial process intrinsic to schizophrenia.

From the clinical perspective, a critical issue is whether or not the deficits in grey matter reported by Sarró et al. might actually be caused by prolonged exposure to antipsychotic drugs. Whether macroscopic changes in brain structure are attributable to antipsychotics is unclear. Both increases and decreases in volume of the basal ganglia have been reported. There have been thought-provoking reports of widespread decreases in cortical grey matter in schizophrenia during long-term treatment with antipsychotic medication, but disentangling effects of greater severity of illness from the direct effects of medication is challenging. Thus, at this stage, the grounds for proposing that the deficit of grey matter associated with tardive dyskinesia might be a direct consequence of antipsychotic treatment are tenuous.

### Conclusion

In conclusion, the evidence that recurrent dyskinesia is a manifestation of schizophrenia, together with the compelling evidence that the intrinsic pathophysiology of schizophrenia is associated with widespread but subtle deficits in the amount of grey matter, supports the hypothesis that the intrinsic pathophysiological process of schizophrenia, acting in brain regions that are engaged in complex motor activity, makes a substantial contribution to the predisposition to tardive dyskinesia. However, comparison of dyskinesia with hallucinations indicates that factors other than the brain regions affected by the intrinsic pathophysiology play a role in the determining predisposition to these two disparate types of symptoms. In particular, age plays a much greater role in dyskinesia and might be a key factor in the observed tardiness. The possibility that treatment with antipsychotic medication might play a direct causal role in the deficit of grey matter reported by Sarró et al. cannot be excluded, but at this stage the evidence for such a role is tenuous.

### References

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