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The Mechanism of Akathisia - Comments on Wu et al. Eur Neuropsychopharmacol 2023;72:40-49

In a recent article in this journal, Wu et al. (2023) describe the results of their systematic literature review of the prevalence of akathisia in controlled clinical trials of initiating monotherapy of 17 antipsychotics in adults with schizophrenia. They focused the accompanying meta-analysis on the relationship between the dosage used and the number of individuals with akathisia. Unfortunately, they refer twice to one of my publications (Loonen and Stahl, 2011; doi: 10.1017/s1092852912000107) under the name Stahl and Lonnen (2011). This is also not very surprising because despite repeated attempts, we never managed to get this corrected by the US National Library of Medicine (NLM) in their MEDLINE database. The EMBASE and Web of Sciences databases do list this publication correctly. I would like to take this opportunity to discuss the described putative mechanism of akathisia in more detail. The human extrapyramidal system can be conceived to consist of three parallel divisions: the amygdaloid, ventral and dorsal systems (Loonen and Ivanova, 2021; Loonen et al., 2019). Phylogenetically, the amygdaloid division is already present in the oldest vertebrates (originated 560 million years ago) and all along it has been composed of the same cellular elements that are therefore found in each division (Stephenson-Jones et al., 2012). These elements are mainly the GABAergic medium spiny projection neurons (MSN) distinguishing a dopamine D2 carrying subtype from the indirect pathway. Other important cellular elements are amongst others the giant cholinergic interneurons and GABAergic fast spiking interneurons. Akathisia mainly involves the ventral extrapyramidal system that includes the nucleus accumbens. Dopamine D2 receptor antagonists disinhibit MSN from the indirect pathway and thereby reduce the output of the extrapyramidal circuits. Within the nucleus accumbens, a distinction must be made between a core part and a shell part (Fig. 1). Only the shell part

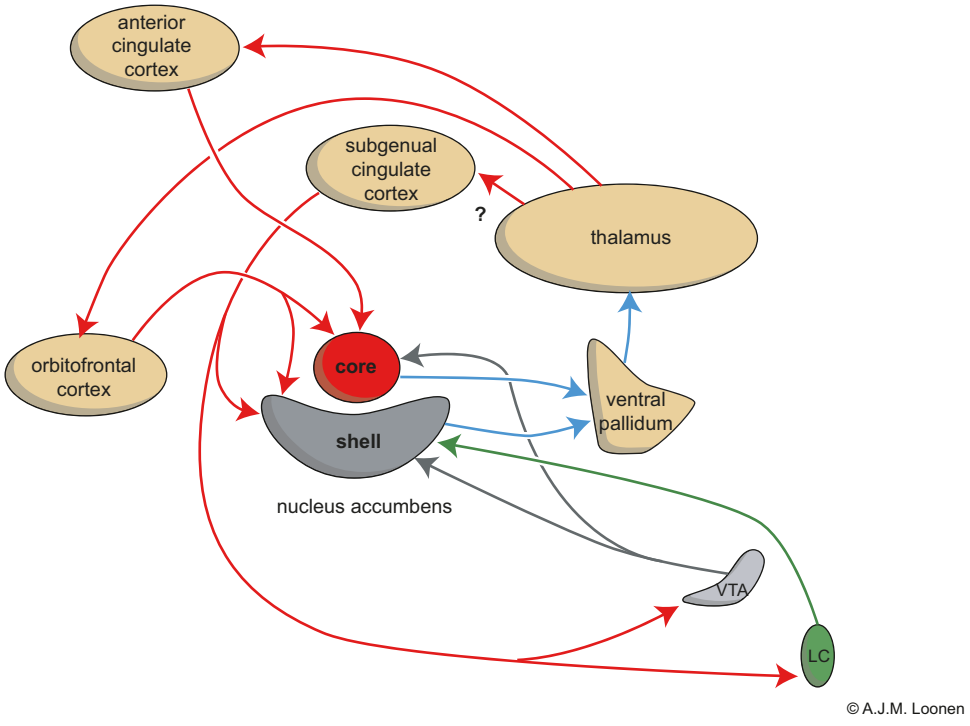

Fig. 1 Scheme of relevant connectivity for causing akathisia within the ventral extrapyramidal system. Note that β-adrenergic input stimulates only the shell part of the nucleus accumbens. VTA, ventral tegmental area; LC, locus coeruleus. Red arrows, glutamatergic; blue arrows, GABAergic; gray arrows, dopaminergic; green arrow, adrenergic.

is also innervated from the adrenergic locus coeruleus via β adrenoceptors with a net activating effect (Loonen and Stahl, 2011). Upon blockade of dopamine D2 receptors, compensating adrenergic activation of the shell part creates the urge to get moving. The activity of MSN of the indirect pathway can be reduced with anticholinergics and 5-HT2C antagonists and the activity of adrenergic projections with β-blockers. Therefore, this model explains the therapeutic effect of these agents in akathisia. For more details, please refer to several previous publications. I greatly appreciate the work of the authors and hope to be of support in finding explanations for the differences between the 17 antipsychotics by describing the model presented earlier.

Declaration of Competing Interest

The author declares no conflict of interest related to this work

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