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# We're not in Kansas anymore: ectopic dopaminergic terminals as an explanation for the positive symptoms in psychiatric pathology

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Psychiatric disorders currently comprise more than 5% of the total disease burden worldwide,<sup>1</sup> a share that is expected to increase as familiarity with guidelines for diagnosis becomes more widespread and the stigma associated with mental disorders continues to decrease. A number of mental disorders have been identified that have, maybe only temporarily, a high dopamine release component in brain regions associated with those disorders. Several of them, including schizophrenia, bipolar disorder, obsessive-compulsive disorder, Tourette syndrome and stuttering, respond well to antipsychotics or include antipsychotics as part of standard treatment.<sup>2,3</sup> A common feature of these disorders is that blockade of postsynaptic dopamine receptors is proven to alleviate the most prominent positive symptoms. However, the more fundamental question is, where is all the extra dopamine coming from?

Possible mechanisms for the abnormally high dopamine release have been proposed previously, but none have been conclusively validated, nor are they generalizable across multiple disorders. In brief, these include increased firing of dopamine neurons, a functional defect in dopamine reuptake from the synaptic cleft, and alterations in postsynaptic dopamine receptor expression and signalling.<sup>4-6</sup> These mechanistic interpretations were developed under the assumption that long-distance axonal pathfinding, most of which occurs during embryonic and fetal development, has ended by early childhood, generally before the onset of the first symptoms in any of the psychiatric disorders mentioned above. Recently, Reynolds and colleagues<sup>7,8</sup> and Hoops and colleagues<sup>9</sup> were able to demonstrate that, in mice, anterograde axon pathfinding of mesocortical dopamine neurons continues throughout adolescence, a finding not yet directly replicated in humans, but likely only because of the difficulty of doing equivalent experiments with human participants. In line with these findings, there has been some indirect evidence from nonhuman primates that showed the number of dopaminergic inputs in the prefrontal cortex (PFC) increases from adolescence to

adulthood.<sup>10-12</sup> We find the coinciding timing of adolescent anterograde dopaminergic pathfinding and the onset of symptoms in many of these hyperdopaminergic psychiatric disorders intriguing to say the least. In this editorial, we raise the possibility that alterations in dopamine axon targeting and growth in adolescence may be a key contributor to mental illnesses, particularly those with an onset in adolescence.

The ventral tegmental area (VTA) is the principal source of mesocorticolimbic dopaminergic terminals in the mammalian brain, with the mesolimbic pathway innervating primarily the ventral striatum and the mesocortical pathway innervating primarily the PFC. While neuronal input subgroups from other neuromodulatory systems<sup>13-15</sup> achieve their final long-distance connectivity to the cortex by early postnatal life, the mesocorticolimbic dopamine system continues to mature well into adulthood. In rodents, dopamine axons destined to innervate the ventral striatum reach this region by early adolescence; however, mesocortical dopamine axons pass through this region and continue to grow toward the PFC throughout adolescence. Arrival of these latter dopaminergic terminals, and their subsequent synapsing in the PFC, coincide with behaviours that are refined in adolescence.<sup>16</sup> In fact, the dopaminergic network in the brain has been previously described as a "plasticity network"<sup>17,18</sup> that allows for local rewiring in response to environmental stimuli well into adult life. Recently, 2 studies<sup>19,20</sup> have expanded on earlier histological descriptions of the rodent VTA and have resolved multiple different subpopulations of neurons,<sup>21</sup> mostly dopaminergic. This finer division, contingent on transcriptomic identity, may prove useful in elucidating why some populations of dopaminergic neurons in the VTA complete their axonal pathfinding during embryonic and fetal life, while others undergo this process in the juvenile period or, exceptionally, as late as adolescence. These different neurodevelopmental timelines of dopaminergic axon pathfinding may help explain the various permissive periods of neuroplasticity in postnatal life.

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**Cite as:** *J Psychiatry Neurosci* 2023 February 21;48(1). doi: 10.1503/jpn.230015

In adolescent rodents, mesocortical dopamine terminals advance from the VTA through the nucleus accumbens and terminate in the PFC. It is conceivable that a number of these terminals can deviate from this intended target, either for genetic or environmental reasons, and synapse in unintended locations.<sup>7,8</sup> At these aberrant sites, where dopaminergic axons are normally scarce or absent, there is now abnormal and elevated dopamine release. Khlghatyan and colleagues<sup>22</sup> used a high-sensitivity approach to map D2 receptors in the human cortex and showed both widespread low-level cortical expression and multiple foci of D2 receptor clustering in areas not previously considered for significant dopamine signalling (insula, somatosensory, visual and auditory cortices). This shows that there are several brain areas that can detect/encode subtle changes in dopamine signalling and that ectopic dopaminergic fibres that happen to intercede will likely be integrated into the local circuitry.

We posit that in the hyperdopaminergic disorders mentioned previously, and likely many others, a part of the pathology could be explained by dopaminergic terminals deviating from their intended target and ectopically innervating other brain areas. At these loci, the inclusion of aberrant dopamine signalling would alter the normal activity of the circuitry.<sup>23,24</sup> In addition, the VTA has a finite number of dopaminergic cells, all of which have an intended and most likely unique neuroanatomical site, as few mesocorticolimbic dopaminergic neurons in rodents show collaterals.<sup>7,25–29</sup> Ectopic dopamine terminals would no longer be available to synapse their intended target, as in the neurotypical brain, since they would now innervate an erroneous brain region. We suggest that the intended target of these terminals will have reduced dopamine innervation and present its own dysfunction,<sup>7,8</sup> an additional insult stemming from the rerouting phenomenon, although some degree of compensation in local circuitry may occur. This interpretation is intriguing as it could help explain the dichotomy of symptoms often seen in some psychiatric disorders, namely positive and negative symptoms or, more simply, domains of hyperfunction and hypofunction. With that being said, many of the findings from studies in rodents need to be substantiated in humans, the constellation of symptoms is broad, and multiple other brain regions are implicated.

The following examples of psychopathological features are in line with our interpretation. A reported 60%–80%<sup>30</sup> of patients diagnosed with a schizophrenia-spectrum disorder experience auditory hallucinations; however, they are also present in other mental disorders, such as bipolar depression (prevalence of 20%–50%), PTSD and major depression.<sup>31</sup> These hallucinations are called *paracusias* and the underlying cause provoking them is not understood. Functional MRI (fMRI) studies have found both increased spontaneous activation of the primary auditory cortex in the absence of an auditory stimulus<sup>32</sup> and decreased activity during stimulus presentation.<sup>33–35</sup> The current interpretation for these seemingly paradoxical findings involves intrinsic stimulation (coming from a different brain area) and reduced extrinsic stimulation that follows the normal progression of the auditory pathway.<sup>33</sup> While several neuroanatomical abnormalities have been found at the level of the Heschl gyrus (the primary auditory cortex<sup>36,37</sup>) and

other associated areas (e.g., inferior part of the Broca area<sup>35,38</sup>), their underlying cause remains elusive. Moreover, there is indirect evidence that dopamine dysfunction is involved in these alterations.<sup>39</sup> The major prevalence of auditory hallucinations in schizophrenia marks it as its most reliable feature<sup>40,41</sup> and makes understanding them a stepping stone to elucidating the neurobiology of dopaminergic pathologies. One likely source of additional synaptic input into the Heschl gyrus may be ectopic dopaminergic axons, which could explain the dopaminergic bias of auditory hallucinations and the adolescent timeline of symptom onset.

Another common positive symptom often experienced by patients with schizophrenia-spectrum disorder is olfactory hallucination, with a lifetime prevalence of 35%<sup>42</sup> and a past-month prevalence of up to 17%. The experience of smell is often not benign, but usually malodorous (e.g., rotten eggs, feces, diesel) and represents a type of phantosmia called *cacosmia*.<sup>43</sup> The smell is a source of distress for the patient,<sup>44</sup> as it seemingly follows the patient from room to room and cannot be escaped, leading to decreased food intake, low mood and further pathology. Olfactory hallucinations are associated with poorer outcomes in patients with schizophrenia,<sup>45,46</sup> but standard antipsychotic treatment works well to reduce and abolish the sensation of *cacosmia*.<sup>47</sup> While the source of this phenomenon can be placed along the olfactory tract, the proximity of the olfactory tubercle and the piriform cortex to the nucleus accumbens make them stand out. If we consider *cacosmia* through the lens of aberrant anterograde dopaminergic pathfinding, it is plausible that dopaminergic axons originating in the VTA and passing through the nucleus accumbens can deviate and synapse erroneously in an olfactory area.<sup>48,49</sup> Alterations in the olfactory dopaminergic system itself<sup>50</sup> may also be at play, although maturational processes occurring in this system in adolescence, if any, remain to be elucidated. From the clinical perspective, in the average psychiatric patient, the onset of *cacosmia* occurs around age 19 years<sup>51</sup> as a random occurrence unrelated to other stimuli, and it gradually worsens in the absence of treatment. We suggest that this sequence of events follows closely a situation in which dopamine axons could begin ectopically innervating these regions, possibly during adolescence, with more inputs occurring with advancing time.

Adolescence is a time of increased social and environmental exploration and interaction. During adolescence, males and females experience increased circulating sex hormones,<sup>52,53</sup> which are well known for their altering effects on gene expression. Sex hormones have previously been suspected in the pathogenesis of psychiatric disorders owing to disease onset occurring shortly after puberty.<sup>54</sup> For example, in individuals with schizophrenia,<sup>55</sup> obsessive-compulsive disorder<sup>56</sup> or bipolar disorder,<sup>57</sup> the onset of symptoms begins in mid to late adolescence,<sup>58</sup> a few months to a few years after the increase in sex hormones experienced at the beginning of puberty. Among their pleiotropic effects, sex hormones have long been shown to modulate dopamine transmission in the brain,<sup>59–61</sup> with multiple mechanisms proposed to explain these findings. We suggest that sex hormones may trigger or stimulate the last period of anterograde dopamine axon growth, likely in conjunction with alterations in circulating human growth hormone and insulin.<sup>62,63</sup>

## Conclusion

We propose the interesting possibility that altered dopaminergic states, as seen in some psychiatric disorders, may be explained, in part, by anterograde dopaminergic terminal migration and mistargeting occurring in mid to late adolescence. As this finding has been shown only in mice, it remains to be validated in humans; however, the coinciding timing of this phenomenon and the age of onset of altered dopaminergic psychiatric disorders is difficult to ignore. We posit that dopaminergic mistargeting may account, in part, for the presence of positive symptoms and that a reduction in terminals from intended targets may explain some of the negative symptoms and cognitive deficits observed in individuals with these disorders.

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**Funding:** The work and authors were supported by the National Institute on Drug Abuse (Grant number: R01DA037911), the Canadian Institutes of Health Research (Grant Number: MOP-74709) and the Natural Science and Engineering Research Council of Canada (Grant Number: 29822268).

**Competing interests:** None declared.

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