Review of: "Dopamine D5 receptor involvement in LTD and LTP: adjustment to the dysconnectivity theory of schizophrenia"

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This manuscript addresses the interesting role of dopamine D5 receptors in the neuroplasticity that might play an important role in persistent symptoms and disabilities in schizophrenia. It is a selective review of the literature, drawing on evidence from a very small number of studies. While the underlying concepts are interesting, the quality of the scholarship is disappointing.

For example, the Introduction introduces more than 20 distinguishable ideas, but there is only a single reference (to Hansen et al[1]), provided at the end of the Introduction. Earlier in the introduction Labrou refers to 'the authors'. I presume that here he is referring to Hansen et al . However, the multiple different ideas presented in the Introduction are not direct quotations from Hansen et al. It is unclear whether or not these ideas reflect the views of Labrou himself; Hansen et al, or the authors of papers reviewed by Hansen. The reader has no way of establishing the nature or strength of the evidence for the many ideas expressed by Labrou, without embarking of a careful reading of Hansen et al and the literature quoted by Hansen et al.

Similarity in section 2, addressing the D5R and inflammation, the second paragraph begins with the sentence 'In the current article, the authors performed an experiment with wild type mice and mice that were knockout for the D5 gene wild type' Here it appears that 'the authors' are the Xing Liu et al[2] to whom Labrou provides reference at the end of a long paragraph expressing multiple ideas. The third paragraph also refers to Xing Liu et al. However it is not clear whether crucial sentences such as 'This suggests that in schizophrenia, there is some degree of susceptibility to ROS, due to the dysregulation of the D5R.' reflects the views of Xing Liu et al, based on their study of mice, or the views of Labrou, based on unreferenced evidence for inflammation in humans with schizophrenia.

Other statements are simplistic. For example, Labrou's unreferenced statement 'FMRI has been recently evaluated as more detailed and accurate over the PET scan, in terms of assessing the condition of the patient, suffering from a mental disorder' might be valid in relation to studies of functional connectivity, but fails to acknowledge that PET studies of both pre- and post-synaptic aspects of dopamine transmission, are more informative than fMRI regarding dopamine dysfunction, which is central to Labrou's manuscript. (See for example, Jaugur et al[3])

Other statements that might best be supported by a reference to a comprehensive review are instead supported by

reference to one or two specific studies that address only specific aspects of the issue. For example, Labrou provides two references covering limited aspects of the topic of heterogeneity, to support his statement: 'After all, since there is heterogenicity among patients, the fact that there is a spectrum, rather than a single phenotype, justifies the term 'set of disorders'.' The topic of heterogeneity of clinical presentation in schizophrenia has been described extensively by many authors, starting with the classical descriptions by Bleuler and Kraepelin. Crow's two syndrome model[4] is relevant to the ideas expressed by Labrou. Many subsequent investigators since have addressed relevant aspects of heterogeneity.[5,6]

If we set aside the frustrating lack of detail about the nature, quality and replicability of the evidence supporting Labrou's statements, some of the ideas he expresses are thought provoking. He points out that an abnormality of plasticity might account for the persistence of paranoid ideas and also for memory impairments. The persistence of delusions despite treatment with dopamine blocking medication in some cases, is of substantial clinical importance. Similarly, cognitive impairments, including memory impairments, respond poorly to current treatments. However, Labrou fails to discuss the evidence regarding the relationship between persisting delusions and cognitive impairment. Metanalyses of the relationship between symptoms and cognitive impairment reveal relationships of only modest strength in schizophrenia (For example, Ventura et al[7]). However studies that have focused explicitly on cases with persisting symptoms or disability do report stronger relationships between specific symptoms and cognitive impairments.[8,9] However, these studies report relationships between cognitive impairment and either disorganization or negative symptoms. In contrast, the correlations with persisting delusions and hallucinations reported in those studies are weak. The studies that have investigated brain mechanisms underlying persistent symptoms and cognitive impairment (for example, Palaniyappan et al[10]; Briley et al[11]) report abnormalities in widespread cortical regions. As Labruo notes, frontal cortex, corpus striatum and hippocampus are linked within networks that are likely to be implicated in the mechanism of schizophrenia. He places emphasis on the hippocampus. Evidence such as that provided by Palaniyappan et al[10] and Briley et al[11], might be indirectly relevant to hippocampal plasticity, but might also reflect plasticity in other brain regions.

In summary, Labrou raises the interesting possibility that D5 receptors might play a role in the impairment of plasticity underlying persisting symptoms and disabilities in schizophrenia, but he provides only a superficial account of the relevant evidence.

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