



## Review

## NMDA receptor hypofunction and the thalamus in schizophrenia



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## HIGHLIGHTS

- Higher order (HO) thalamic relays transmit copies of cortical motor instructions.
- HO thalamic nuclei are affected in schizophrenia.
- Schizophrenia involves a failure of internal motor monitoring mechanisms.
- NMDAR hypofunction in schizophrenia may impair the function of HO nuclei by attenuating driver inputs from the cortex.

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## ABSTRACT

The thalamus can be subdivided into two kinds of nuclei, the higher order (HO) and the first order (FO) relays, which are distinguished based on the origin of their main or driver inputs. The driver inputs to the HO nuclei arrive from the cortex, and the messages they deliver are then relayed to other cortical areas. As the origin of these inputs is the cortical layer V, whose axons branch and innervate lower motor centers in the CNS, the messages are copies of motor instructions issued to those lower motor centers. These copies are thus an integral part of perceptual processes. In schizophrenia, the HO nuclei are shrunken suggesting that a reduced ability to integrate copies of ongoing motor commands in perceptual processes may be one part of the underlying pathophysiology. The driver inputs in the thalamus utilize ionotropic glutamate receptors such as the NMDAR. NMDAR antagonists may exert their pro-psychotic effects by impairing the function of the HO nuclei. Here, we argue that such agents (or the proposed NMDAR hypofunction in schizophrenia) weaken the driver inputs in the HO nuclei, thereby producing a cortico–thalamo–cortical disconnection and impairing sensorimotor integration.

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## 1. Introduction

The N-methyl-D-aspartate receptor (NMDAR) hypofunction model has been influential in schizophrenia research over the past several decades [17]. This model is supported by observations that NMDAR antagonists can cause psychosis and other related behavioral and cognitive

abnormalities in humans and animals. There are a number of proposed mechanisms whereby this may occur, which will be briefly discussed (Carlen et al., 2012) [8]. The purpose of this review is to present another potential explanation for how NMDAR antagonists exert their psychotogenic effects, which is not mutually exclusive with the other existing models. The value of the mechanism that will be presented here is that it attempts to integrate the NMDAR hypofunction hypothesis with the pattern of thalamic abnormalities reported in schizophrenia [7]. Namely, There is evidence that NMDAR antagonist pro-psychotic

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effects are mediated by their action in the thalamus [19]. The concepts that will be introduced in this theoretical review center on (1) the function of the thalamus, (2) how this function might be impaired by NMDAR antagonists (or its hypofunction in schizophrenia) and (3) how this could lead to psychosis and other associated deficits, such as disorganization of behavior.

It is increasingly becoming recognized that the thalamus is composed of two kinds of relays: the first order (FO) and the higher order (HO) relays, which differ with respect to their connectivity and function [29]. The FO relays receive their main inputs from the sensory periphery and other non-cortical sources, while the main inputs to the HO nuclei originate in the cortex. Therefore, the HO nuclei are thought to function as a hub for cortico–cortical interactions. It is significant that in schizophrenia, the HO nuclei have been found to be structurally affected, while the FO nuclei are relatively intact [7,29]. As argued in earlier papers [35–40], this finding along with reported sleep-related brain rhythm abnormalities [12] suggests that schizophrenia involves impaired transthalamic cortico–cortical communication. The resulting disconnection between different cortical areas may lead to an inability to recognize self-initiated motor output as such (i.e., source monitoring deficits). The failure to recognize the sensory consequences of self-initiated actions is proposed to then lead to its attribution to outside sources, which may in turn underlie some psychotic experiences [11, 13]. In the following sections, the concept of HO thalamic nuclei and their significance for schizophrenia will be explained in greater detail, and it will be outlined how the proposed NMDAR hypofunction may fit into this novel neurobiological model of psychosis.

In our previous work, we have argued that schizophrenia involves a dysfunction of the thalamic T-type calcium channels, which were found to be important for the function of the HO nuclei [24]. This may in turn impair transthalamic cortico–cortical interactions. Here we argue that NMDAR hypofunction/blockade may likewise impair such interactions by attenuating the main inputs in the HO thalamic nuclei, thereby causing some of the deficits observed in psychosis.

## 2. Higher order thalamic nuclei: their connectivity and function

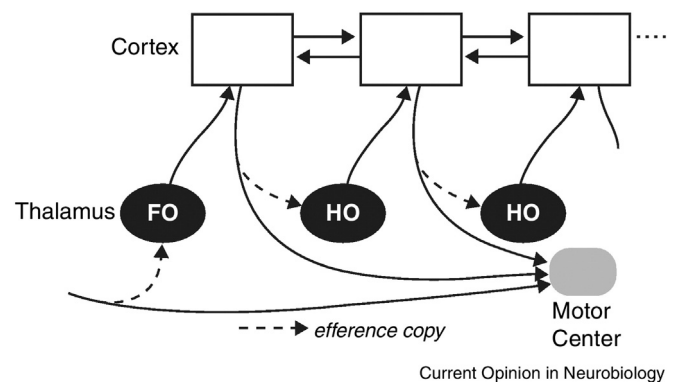
The inputs to the thalamus can be classified into two categories. The driver inputs represent the main information route and a number of features distinguish them from neuromodulatory inputs. For example, the driver inputs have larger and more proximal terminals, thick axons; they utilize ionotropic glutamate receptors (such as the NMDAR) and produce larger postsynaptic potentials [28]. Remarkably, the driver inputs share these features regardless of their source (e.g., cortex, sensory pathways, mammillothalamic tract, deep cerebellar nuclei) [27]. They are less numerous than the modulatory inputs, and importantly, most and possibly all of them have branches that also innervate lower motor centers in the brainstem. In contrast, the neuromodulatory inputs to the thalamus have smaller and more distal terminals, thin axons; they tend to utilize ionotropic and metabotropic receptors for different neurotransmitters (including metabotropic glutamate receptors) and produce smaller postsynaptic potentials. Corticothalamic neuromodulatory inputs originate in the cortical layer VI and innervate both the HO and the FO relays. The focus in the remainder of this paper will be on the driver inputs.

The driver inputs to the HO thalamocortical relays arrive from the cortex (more specifically the motor cortical layer V), and the driver inputs to the FO nuclei arrive from areas other than the cortex (e.g., ascending sensory pathways, cerebellum) [27,29]. In other words, the FO thalamocortical relays transmit information to the cortex that no other part of the cortex has received prior to that, while the HO relays transmit information that has already been processed by at least one cortical area. In fact, for some thalamocortical inputs that pass through HO relays, this could be second, third or more run through thalamocortical loops. Furthermore, as the driver inputs to the HO relays arrive from the pyramidal neurons in the cortical layer V, which branch and also

innervate lower motor centers in the CNS, the HO nuclei are in the position to inform other cortical areas about ongoing motor instructions being issued by a particular cortical area. This novel conceptualization of thalamic function is valuable as it reveals a pattern whereby copies of motor commands issued by a cortical area are transmitted to other cortical areas in an ongoing manner via a transthalamic route. The exact role of these copies for cognitive processes such as perception is still unknown, but the discussion that will follow below about what occurs in schizophrenia (and/or NMDAR hypofunction) may shed some light on the functional role of this dynamic system.

The other candidate pathways that may be involved in the transmission of copies of ongoing motor commands between different cortical areas are direct cortico–cortical links [28]. However, the direct cortico–cortical pathways reside entirely in the cortex, while, as already mentioned, the cortical layer V neurons that provide the driver inputs to HO nuclei also branch and innervate lower motor centers in the brainstem and the spinal cord. Therefore, transthalamic cortico–cortical links are in a unique position to aid in the integration of motor commands with resulting sensory inputs into a perceptual whole. Moreover, the transthalamic cortico–cortical pathways have been found to provide a crucial information route between cortical areas [31]. Therefore, any disruption of the transthalamic pathways is likely to have far reaching consequences by dissociating sensory processes from ongoing motor outputs, and thereby possibly resulting in psychotic experiences such as for example delusions of control (i.e., belief that one's own actions are controlled by alien forces).

Note that the discussion above contains references to FO nuclei and HO relays, respectively. This is because the FO nuclei tend to almost exclusively contain thalamocortical neurons whose driving inputs are of ascending, non-cortical origin. One example of a FO nucleus is the lateral geniculate nucleus (LGN), which receives retinal driving inputs. In contrast, the HO nuclei (such as the mediodorsal nucleus or MD) contain a proportion of FO inputs, and therefore, the term HO relays is more appropriate. One intriguing recently reported possibility is that some thalamocortical neurons receive both FO and HO inputs [16], which is consistent with other reports that suggest that the HO relays (particularly in the MD nucleus) have a role in sensorimotor integration [14,30,41]. Moreover, it has been shown that cerebrovascular accidents that affect the HO nuclei result in a failure of sensorimotor integration [3,23] and to source-monitoring deficits, whereby own errors during the performance of various tasks were attributed to outside



**Fig. 1.** Cortico–thalamo–cortical circuits (adapted with permission from [28]). The cortical layer V pyramidal neurons issue motor commands to motor centers in the brain stem and the spinal cord. Some of them branch off and innervate the higher order (HO) thalamic relays. As the cortical layer V is motor in nature, the inputs these collaterals provide to the HO relays are likely copies of ongoing motor commands (efference copies). The HO relays in turn relay this input to other cortical areas, which enables sensory cortical areas to recognize self-initiated motor output as such. The HO nuclei are affected in schizophrenia suggesting that this mechanism is impaired in psychosis. NMDAR antagonists (or NMDAR hypofunction in schizophrenia) may cause psychotic symptoms by attenuating the transmission of efference copies, as the layer V inputs to the HO relays are driver inputs, which rely on ionotropic glutamate receptors such as the NMDAR.

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