An Introduction to the Nucleus Accumbens in schizophrenia

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A B S T R A C T

The Nucleus Accumbens is one of the basal ganglia and has been implicated of the pathophysiology of disorders such as depression and schizophrenia. It's involvement in these disorders is fundamentally due to its role in the cortico-ganglia-thalamic loop. The Nucleus Accumbens receives dopaminergic inputs critically important in schizophrenia and is as key point of action of antipsychotic medication, yet it has very little research into neuropathological or functional changes. The research that does exist has produced directly contradicting results, with most of the repeatable findings coming from animal models of dopaminergic dysfunction

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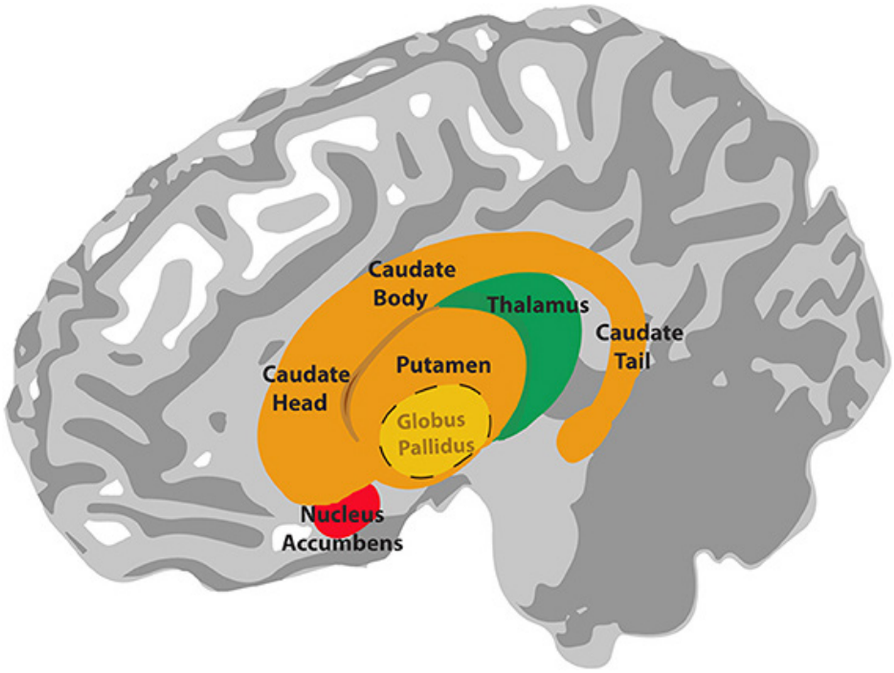
Historically the Nucleus Accumbens (NAcc), one of the key basal ganglia nuclei, has been of interest in neuropsychiatric due to its proposed role in addiction, particularly morphine, cocaine and amphetamine, thought to be due to drug-mediated release of dopamine from the ventral tegmentum areas during substantial nigra. More recently nicotine addiction has been suggested to work through this pathway (Pontierri *et al*, 1995; Pierce & Kalivas, 1995).

The NAcc is a Basal Ganglia nucleus, sometimes described as part of the ventral striatum although it is distinct from the two primary striatal nuclei, the caudate and putamen, and is a central part of the cortico-ganglia-thalamic loop (Yager, 2015). The NAcc is directly continuous with the main dorsal part of the striatum, and often described as part of the striatal complex. However, it has some structural distinction, as compared to the putamen and caudate, as it is split into a core and a shell (Zaborsky *et al*, 1985). The core is largely continuous with the rest of the striatum and is composed of similar spiny neurons which predominantly form the output neurons of the NAcc, although the shell has independent projections to the bed nucleus of stria terminalis and lateral hypothalamus (Zaborsky *et al*, 1985; Groenewegen *et al*, 1989).

The NAcc also receives a distinct collection of dopaminergic neurones directly from the ventral tegmentum area, the dopaminergic nucleus that lies adjacent to the substantia nigra. This is known as the mesolimbic pathway and has been strongly implicated in addiction (Cristicelli & Avena, 2016). Whilst the main output structure for striatal medium spiny neuron axons is the thalamus, although major pathways also project to the globus pallidus and the NAcc, as well as reciprocal projections back to the dopaminergic regions of the ventral tegmentum area and substantia nigra (Shepherd, 2013). There is a reciprocal feedback loop of GABA projections from the NAcc to the ventral pallidum and ventral tegmentum area, and receives glutamatergic projections from the prefontal cortex, hippocampus and amygdala. The amygdala glutamatergic projection to the NAcc in particular has been suggested as key in modulating cue-triggered motivated behaviours (Cador *et al*, 1989), and the prefrontal cortex regulates NAcc dopaminergic output by glutamatergic projection (Jackson & Moghaddam, 2001). Hippocampal projections to the NAcc arise from the sibuculum, the most inferior part of the hippocampal formation, lying between CA1 and the entorhinal cortex. The ventral subiculum exerts a strong regulatory role on activity of dopaminergic projections from the ventral tegmentum area via glutamatergic mechanisms localized within the NAcc (Floresco *et al*, 2001; Bagot *et al*, 2015).

The precise pattern of inputs to the NAcc is complicated, but the projections from the cortex, thalamus and amygdaloid are topographically organised (see Groenewegen *et al*, 1987 for review), meaning that only in limited parts of the nucleus do interactions between these inputs occur.

The very large ENIGMA project scanning over 2,000 schizophrenic brains compared to more than 2,500 controls showed the NAcc was smaller in schizophrenia, as well as similar findings in smaller studies (Ebdrup *et al*, 2010; Rimol *et al*, 2010). Although this has not been consistently reported in large imaging studies, with striatal volumes, including the NAcc, showing no change I in schizophrenia (Bogerts et al., 1985). The NAcc has had only limited neuropathological attention in schizophrenia. Consistent with some imaging findings there is a 42% decrease in NAcc volume 50% decrease in total neuron



The location of the Nucleus Accumbens relative the striatum and thalamus (Lim *et al*, 2014).

number (Pakkenberg, 1990; Lauer et al., 2001), but again this is in contrast to other studies of the same regions showing no changes (Lesch and Bogerts, 1984). Post-mortem studies have mostly suggested that the NAcc shows no overall change in volume in schizophrenia, although one small scale stereological study did report an overall increase in NAcc size (Lauer *et al.*, 2001; Gunduz *et al*., 2002; Kreczmanski *et al*., 2007; Ballmaier *et al*., 2008). The right NAcc and caudate higher neuron numbers in schizophrenia (Beckmann and Lauer, 1997), with another study showing no change in NAcc neuron number (Kreczmanski et al., 2007). The possible causes of such strongly-conflicting results may well be down to the stereological methods (von Bartheld, 2002), or heterogeneity of samples that is so common in this field.

As mentioned previously, the NAcc has a potentially important role in the biology of schizophrenia as it is part of a complex processing loop of cortico-striato-nigral-thalamo-cortical circuits (Haber, 2003), which has been assumed to be a prime system for the elevated dopamine levels in schizophrenia, based on its functional properties and evidence of antipsychotic drug action therein (Deutch *et al*., 1992; Merchant and Dorsa, 1993). Dopamine turnover was not increased in schizophrenic patients but, as assessed by the spiroperidol-binding technique, there was a significant increase in postsynaptic receptor sensitivity. The change in the dopamine receptor occurred in NAcc, putamen, and caudate nucleus (Owen *et al*., 1978; Mackay *et al*., 1982). Initially studies found no change in possible dopamine-receptor sensitivity in the NAcc, but one later neuropathological study has reported potential decreased dopamine sensitivity change (Crow *et al*., 1978; Hetey *et al*., 1991). Ultrastructural examination of NAcc synapses shows a 19% increase in the density of asymmetric axospinous synapses in the NAcc but not the in the shell in schizophrenia. Similarly postsynaptic densities of asymmetric synapses had 22% smaller areas in the core NACC but again not in the shell, suggesting increased excitatory input to the NAcc core in schizophrenia (McCollum et al., 2015).

Dopamine D_3 receptors are located predominantly in the intermediate shell, the primary area of thalamic input (Diaz *et al*, 1995), and consistent with this the shell rather than core appearing to be the target of antipsychotic action (Deutch *et al*, 1992; Merchant & Dorsa, 1993). Amphetamine administration yields an NAcc neurotensin response which can be blocked using a dopamine D_1 antagonist, suggesting a physical as well as functional variation in dopamine receptors subtypes throughout the NAcc. These differing regulatory pathways moderated by dopamine receptors clearly have significant implications for the role of antipsychotic medication in schizophrenia treatment.

The NAcc has also been shown to be involved in stress-activated activation of the dopamine system, and thus may be related to schizophrenia symptoms influenced by stress. Information transfer from ventral to dorsal striatum, essentially the mesolimbic pathway, relevant to antipsychotic medication depends on both striato-cortico-striatal and striato-nigro-striatal sub-circuits, yet although the functional integrity of the former appears to track improvement of positive symptoms of schizophrenia, whilst the latter have received little experimental attention in relation to the illness. Compared with non-refractory patients, treatment-resistant individuals exhibited reduced connectivity between ventral striatum and substantia

nigra. Furthermore, disturbance to corticostriatal connectivity was more pervasive in treatment-resistant individuals (white et al, 2015). Controlled treatment of antipsychotic medication in rats such as haloperidol shows significant intermediate-early gene mRNA in the striatum, particularly strongly in the NAcc. In contrast clozapine produces a similar Fos response in the NAcc but not the rest of the striatum (Deutch *et al*, 1992; Merchant & Dorsa, 1993).

As with the other basal ganglia, the role of the NAcc is poorly understood given its clear critical role in both the pathophysiology of schizophrenia and in the role antipsychotic medication plays in treatment of the disorder. Further examination is needed in this structure, and the associated subcortical networks, to better target future treatments.

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