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Comments and Controversies

Do we need to revise the tripartite subdivision hypothesis of the human subthalamic nucleus (STN)?

Anneke Alkemade, Birte U. Forstmann*

Cognitive Science Center Amsterdam, University of Amsterdam, Netherlands

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ABSTRACT

The exciting development of ultra-high resolution 7 Tesla (T) magnetic resonance imaging (MRI) has made it possible to clearly visualize and delineate the subthalamic nucleus (STN). Ultra-high resolution MRI provides a first step in the ongoing improvement of imaging techniques rendering it likely that in the near future specific subareas of small brain nuclei such as the STN can be visualized. These developments can contribute to improve clinical imaging, allowing even more accurate targeting of the STN. This is interesting in view of putative limbic, associative, and sensomotoric subdivisions within the STN. The concept of anatomically distinct subdivisions is attractive, both from an anatomical as well as a clinical perspective. However, we argue that the current leading hypothesis of three STN subdivisions is based on low numbers of clinical observations and primate tracing studies. 7 T imaging provides us with markers that could potentially help us to distinguish subdivisions, but our preliminary findings do not indicate the existence of subdivisions. In our opinion additional research is needed. As a consequence the tripartite hypothesis should therefore still be a topic of debate. In view of the possible clinical implications, we would like to raise the question whether anatomical evidence on the topological organization within the STN points towards delineated subdivisions, or an organization without strict anatomical boundaries or septa. The latter would require a revision of the current tripartite hypothesis of the human STN.

The STN is a small but important brain structure within the basal ganglia. It plays a crucial role in sensorimotor, cognitive, and limbic functions (Temel et al., 2005). The STN serves as a surgical target for deep brain stimulation (DBS) to provide symptomatic relief in a number of movement disorders refractory to pharmacological intervention (Rughani et al., 2013). Interestingly, DBS of the STN in addition to its clear effects on sensomotoric functions also can cause apathy, compulsivity, hypersexuality, cognitive dysfunction, as well as clinical depression including suicidal ideation (Temel et al., 2005). These effects have been ascribed to the existence of putatively anatomically distinct, sensomotoric, cognitive, and limbic subparts of the human STN (Parent and Hazrati, 1995a, b), although an alternative explanation for the effects of DBS may be the interferences with serotonergic signaling by high frequency stimulation (Navailles et al., 2010; Temel et al., 2007). Additionally, we cannot exclude that cell groups and fibers outside the STN may be affected (Mundinger, 1965). According to the tripartite STN division, the dorsolateral part of the nucleus is responsible for sensomotoric functions, the central part of the STN fulfills cognitive functions, and the medial tip is involved in limbic functions. The existence of distinct STN subdivisions forms the current leading hypothesis in STN neuroanatomy, and is attractive from a conceptual point of view. Theoretically unwanted side-effects of STN DBS could be minimized or even prevented by specific targeting of the sensorimotor subdivision of the STN. Although in today's clinical practice, the electric current field is most likely to extend the borders of the STN. One could speculate that with further technical developments of STN imaging techniques, or microelectrode recordings during surgery in patients it will become possible to identify and target these putative STN subdivisions in humans.

However, the literature indicates that the underlying neuroanatomy is more complicated, and it is feasible that the hypothesis of the tripartite STN division represents an oversimplification of the anatomical make-up (for review see (Keuken et al., 2012)). We therefore asked the following questions: Is there conclusive evidence supporting the tripartite organization of subdivisions within the human STN? Or is there a need to revise current hypotheses on the topological organization within the human STN?

Support for the tripartite organization of the STN in humans is largely based on the extrapolation of studies in nonhuman primates, on a number of clinical observations, and a recent study using diffusion weighted imaging in humans (Haynes and Haber, 2013; Lambert et al., 2012; Parent, 1990; Temel et al., 2005). Primate studies using tracings to map STN projections have formed the basis for the tripartite hypothesis of the STN. These results of these studies have been interpreted

* Corresponding author at: Cognitive Science Center Amsterdam, University of Amsterdam, Nieuwe Achtergracht 129, 1018WS Amsterdam, Netherlands.
E-mail address: buforstmann@gmail.com (B.U. Forstmann).

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by others in well-cited reviews, contributing to the acceptance of the tripartite subdivision theory (Alexander and Crutcher, 1990; Haynes and Haber, 2013; Joel and Weiner, 1997; Parent, 1990; Parent and Hazrati, 1995a, b). Although extremely valuable, tracing studies are technically challenging and have a number of inherent technical limitations. In addition, large discrepancies exist between individual tracing studies (Keuken et al., 2012). Findings are strongly dependent on tracer injection volume and size of the injection site. Since injection sites are generally small to prevent leakage to adjacent brain structures, anatomical connections may be only partly uncovered, and the size of projection sites may therefore be underestimated. In addition, the number of reported observations in primates is usually limited. A recent, and very extensive study by Haynes and Haber (Haynes and Haber, 2013), provides crucial anatomical detail on the primate STN. This study supports the existence of a topological organization within the STN, although strong overlap between the three proposed functional areas exists (Haynes and Haber, 2013). It should be noted that even though the study by Haynes and Haber is of high quality, it is again based on a limited number (2–4) of observations per injection site, and it remains difficult to determine to what extent observations from nonhuman primates can be extrapolated to the human situation.

One may argue that a lack of anatomical organization does not exclude a functional organization. Clinical observations have shown that a hypomanic state in two patients was caused by stimulation via the DBS contact located in the anteromedial STN. The anteromedial contact, as well as a contact more dorsal improved motor symptoms. Contacts at the boundaries of the STN affected neither behavior, nor motor performance (Mallet et al., 2007). These clinical descriptions argue for topological differences, even though these studies are complicated by variations in electrode positioning (Okun et al., 2005), and variations in the orientation of the electrode or STN axis (Plaha et al., 2006). Apart from clinical observations, to our knowledge, only one study has addressed the tripartite division within the human STN. Lambert and colleagues report conformation for three functional zones in the STN using diffusion weighted imaging (DWI). However, this evidence was only obtained for 14 out of 24 STN's tested in these studies ((Lambert et al., 2012) supplements). Interestingly, a substantial number of STN voxels in all tested STN's met the criteria of more than one functional subdivision. The authors did not provide any information on the spatial location of these specific voxels, but in view of the large numbers of voxels meeting the criteria for multiple subdivisions based on their regional connectivity, it is unlikely that these voxels are exclusively located exactly at the interface between two functional areas, and that these voxels therefore contain connectivity patterns meeting the criteria for more than one subdivision. Although these DWI-studies, for the first time, investigate connectivity profiles in the human STN of healthy subjects, the data shows large variation. In 10 out of 24 STN's there is no evidence for three functional zones within the STN. We feel that the data reported by Lambert et al. may, to some extent, support a topological organization within the STN, but there is no strong support for a tripartite organization.

An alternative approach would be to investigate evidence from the rodent STN, as a model for the human STN. However, data from rodents are difficult to interpret since the STN in rats is an open nucleus with dendrites extending into brain areas outside the STN (Afsharpour, 1985a, b). Contrary to rodents, in primates, including humans, the nucleus is considered to be closed with the dendrites largely restricted to the STN (Rafols and Fox, 1976). In addition to the interspecies differences within the STN, the input and output areas of the STN may also show significant interspecies differences. A recent review of animal models on Parkinson's disease indicates that at present no model is available that faithfully reproduces all features of human Parkinson's disease (Lee et al., 2012). In view of these interspecies differences we are not confident that rodent models will provide us with the answer to our question whether there is a tripartite organization of subdivisions within the human STN.

Although many valuable studies have been published addressing the question whether STN subdivisions are present, the need for further studies on the human STN becomes clear. In addition, the following questions arise: Can the human STN and its putative subdivisions be visualized using techniques available for research and clinical practice within the near future? Will it be feasible to test the hypothesis of a human tripartite STN organization?

With the advent of ultra-high resolution 7 Tesla (T) magnetic resonance imaging (MRI) techniques, it is now possible to visualize the human STN in vivo for research purposes (Cho et al., 2010; de Hollander et al., in press; Forstmann et al., 2010, 2012; Keuken et al., 2013; Massey et al., 2012) (see Fig. 1). However, it will take time before these state-of-the-art imaging techniques can be applied routinely for research as well as diagnostics and surgical planning since 7 T MRI scanners are not widely available. In addition, more research is warranted on MR chemistry. Interesting recent publications indicate that using quantitative susceptibility mapping (QSM) have made it possible to quantify brain iron content (Deistung et al., 2013; Langkammer et al., 2012; Schweser et al., 2011). Other methods such as microelectrode recordings in patients during surgery for identification of subdivisions are also promising (Zaidel et al., 2010). Tracing studies as performed in nonhuman primates cannot be performed in humans for obvious reasons. Recent developments in optogenetic techniques will provide more insight in the molecular events occurring in the STN and are likely to

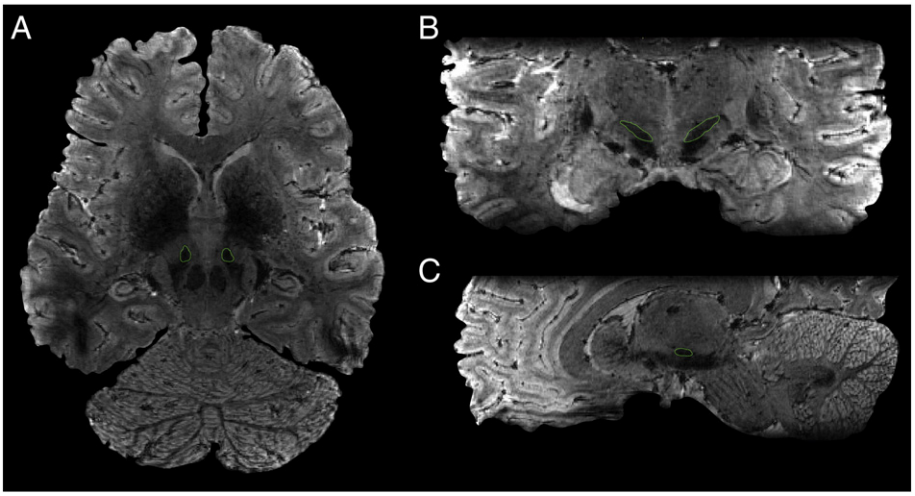

Fig. 1. Illustration of STN visualization using T2*-weighted 0.5 mm^3 isotropic 7 T MRI. A: Transverse view; B: Coronal view; and C: Sagittal view.

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