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Comments and Controversies

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

Christian Lambert[a,*], Ludvic Zrinzo[b], Zoltan Nagy[c,d], Antoine Lutti[e], Marwan Hariz[b], Thomas Foltynie[b], Bogdan Draganski[e], John Ashburner[d], Richard Frackowiak[e]

[a] Clinical Neuroscience, St George's University of London, London, UK
[b] Unit of Functional Neurosurgery, University College London Institute of Neurology, Queen Square, London, UK
[c] Laboratory for Social and Neural Systems Research (SNS Lab), University Hospital Zürich, P.O. Box 146, Rämistrasse 100, CH-8091 Zürich, Switzerland
[d] Wellcome Trust Centre for Neuroimaging, UCL Institute of Neurology, University College London, 12 Queen Square, London WC1N 3BG, UK
[e] LREN, Département des Neurosciences Cliniques, CHUV, Université de Lausanne, Lausanne, Switzerland

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ABSTRACT

Recently in this journal, Alkemade and Forstmann again challenged the evidence for a tripartite organisation to the subthalamic nucleus (STN) (Alkemade & Forstmann 2014). Additionally, they raised specific issues with the earlier published results using 3T MRI to perform *in vivo* diffusion weighted imaging (DWI) based segmentation of the STN (Lambert et al. 2012). Their comments reveal a common misconception related to the underlying methodologies used, which we clarify in this reply, in addition to highlighting how their current conclusions are synonymous with our original paper. The ongoing debate, instigated by the controversies surrounding STN parcellation, raises important implications for the assumptions and methodologies employed in mapping functional brain anatomy, both *in vivo* and *ex vivo*, and reveals a fundamental emergent problem with the current techniques. These issues are reviewed, and potential strategies that could be developed to manage them in the future are discussed further.

It is accepted that the subthalamic nucleus (STN), a small excitatory nucleus within the basal ganglia, is implicated in sensorimotor, cognitive and emotive processing (Parent and Hazrati, 1995; Temel et al., 2005; Yelnik et al., 2007). The specifics of its internal functional organization have roused considerable controversy (de Hollander et al., 2014; Keuken et al., 2012) with an ongoing debate into whether a tripartite division into sensorimotor, associative and emotive regions exists. In a recent comment in this journal, Alkemade and Forstmann have again challenged the evidence for such an organization (Alkemade and Forstmann, 2014). Moreover, their comments and the debate in general raise broader implications into the assumptions and methodologies employed in mapping functional brain anatomy, both *in vivo* and *ex vivo*.

Primate data on tracer connectivity patterns led to the original suggestion of a tripartite division of the STN representing nodes in limbic, associative and motor circuits (Yelnik et al., 2007). In our 2012 paper (Lambert et al., 2012), we showed that such a scheme is also demonstrable in humans using diffusion weighted imaging data *in vivo* at 3T MRI. Rather than assuming a tripartite division, we sought objective evidence from our dataset by plotting the fractional variance across a wide range of clustering solutions, and used an elbow criterion as the decision basis. The main body of the text states that the tripartite division was the optimal solution in 58% of subjects tested. Using this as supportive evidence, we then extracted a tripartite parcellation for each and every individual using ward linkage clustering, a hard clustering technique adopted by many other groups (Bowman et al., 2004; Chen et al., 2012; Palomero-Gallagher et al., 2009; Blumensath et al., 2013; Caspers et al., 2013; Bzdok et al., 2013). Furthermore, we provided individual results for tripartite parcellations for six STN pairs in the supplementary material.

Alkemade and Forstmann state that our study claims to find "*anatomically distinct subdivisions within the STN*". More accurately, our findings suggest distinct regions, or clusters, based on quantifying the similarity between whole brain connectivity patterns using a hard-clustering technique (Gan et al., 2007; Jain, 2010). Whilst connectivity can demonstrate a tripartite subdivision *in vivo*, our discussion explicitly stated that the combined evidence would fit with a model where: "*there are unique limbic and motor STN zones, and that the associative zone represents an overlapping, topographically arranged transition between the two*". This view, derived from the patterns of connectivity *in vivo* at 3T MRI was discussed at length throughout the discussion (for further details readers are referred to "*Associative STN*", "*Topological functional arrangement of the STN*", Fig. 6 and supplementary material 5 from the original paper), and

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* Corresponding author.
E-mail address: clambert112358@gmail.com (C. Lambert).

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was subsequently validated by *ex vivo* primate tracing work (Haynes and Haber, 2013). Given that the original paper actually suggested and provided evidence for the very model now being promoted, we should clarify that our concluding summary statements as cited in their recent article (Alkemade and Forstmann, 2014) should not be taken out of context from the broader discussion originally provided.

The ongoing debate into STN sub-parcellation is symptomatic of a larger, emergent problem in the field of human brain-mapping. Development of advanced imaging techniques with ever-greater resolution allows subdivision of previously defined brain regions into progressively smaller units (Caspers et al., 2014; Caspers et al., 2013; Bludau et al., 2014). This is especially true of white matter connectivity, where graduated overlapping topographic organization seems to exist across many regions (Averbeck et al., 2014; Caspers et al., 2013; Jbabdi et al., 2013). Furthermore, the fact that both graduated and abrupt transition zones are present cortically (Schleicher et al., 1999) and subcortically (Haber et al., 2000) has clear methodological implications beyond those raised in the STN (Alkemade, and Forstmann, 2014). The widely used hard-clustering methods for brain parcellation (Ruschel et al., 2014; Caspers et al, 2013; O'Donnell et al., 2013; Solano-Castiella et al., 2011) will be unable to accurately model or demonstrate graduated architectural features and instead will artificially provide "*anatomically distinct boundaries*" as necessary methodological by-products (Gan et al., 2007; Jain, 2010; Accolla et al., 2014). Techniques that are capable of representing greater degrees of subtlety may ultimately provide more anatomically congruent models, but at the cost of significantly increasing the representational complexity. There is a clear need to develop a coordinate or feature representation system for the brain, with corresponding consistent nomenclature, that will allow accurate mapping and labelling between structures at various levels of parcellation, resolution and scale.

Ultimately, high quality neuroanatomical research in humans is contingent on a constructive dialogue between those engaged in *ex vivo* research defining the underlying architectural properties, and those attempting to model and capture these features using *in vivo* MRI, both at 3T and 7T. Translating these organisational principles across scales and field strengths will yield significant gains both in the understanding of normal cortical function, and the diagnosis and treatment of neurological disease. The answer to the question concerning the most suitable level of parcellation to use will ultimately depend upon the data modality, quality, and intended use. Returning to the STN, the best quality data for surgical targeting, outside specialized research institutes, is obtained from 3T MR machines; therefore using a tripartite schema with tractography may prove clinically useful to improve surgical accuracy by refining DBS lead localization. When 7T MRI systems are more widely available in clinical practice, a finer parcellation schema may well emerge. We look forward to further high-field histological studies from centres that have access to these cutting edge resources, and to future advances in the field and understanding of cortical cartography in general.

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