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A connectivity-based approach to the pathophysiology of hemiballism

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ABSTRACT

Background: Hemiballism may arise as a rare consequence of focal basal ganglia lesions. Pathophysiologically, there is a controversy between the role of the STN as the exclusive lesion localization as opposed to several brain regions in which lesions may induce hemiballism. This is most likely due to a motor circuit affection.
Objectives: To study the affection of neural networks in the pathogenesis of hemiballism.
Methods: We analysed focal vascular lesions inducing hemiballism ($n=8$), their localizations and connectivity profiles. Probabilistic tractography (FSL: http://fsl.fmrib.ox.ac.uk/fsl/) was used to study connectivity.
Results: Lesions inducing hemiballism were distributed across several anatomic regions (basal ganglia, thalamus, caudate, internal capsule) without a clear predilection. However, we detected increased connectivity for these lesions toward the STN and mesial cortical motor regions (pre-SMA/SMA). These regions are interconnected via subthalamo-pallido-thalamo-cortical networks.
Conclusions: We provide evidence for the involvement of the subthalamo-pallido-thalamic pathways in the pathogenesis of hemiballism, which is consistent with data on experimental hemiballism in animals. Electrophysiological basal ganglia recordings and functional MRI would complement our findings to assess the activation patters within these circuits.

1. Introduction

Hemiballism is a hyperkinetic movement disorder characterised by flinging, high-amplitude limb movements restricted to one side of the body [1]. Depending on the amplitude and velocity of movements, hemiballism is often associated with hemichorea and both phenomena are frequently referred to as "hemichorea-ballism" [2,3]. The most frequent cause is stroke and symptoms occur in about 1% of stroke patients [1]. Other etiologies include demyelinating plaques, neoplasms, hyperglycaemia, paraneoplastic proceses and Sydenham's chorea [4].

Hemiballism is an interesting phenomenon insofar as it enables studying a disruption of basal ganglia physiology.

The clinical appearance of hemiballism was reported by Purdon Martin after a focal lesion to the subthalamic nucleus (STN) [5]. Initially, it was called "syndrome of the body of Luys" and was considered to be pathognomonic for STN lesions [5]. However, with the improvement of imaging techniques, focal vascular lesions inducing hemiballism have been detected in many other brain structures, e.g. the thalamus, pallidum, putamen, caudate or even cortical lesions [2,4]. Thus, the initial paradigm of the STN as the exclusive anatomic brain region, where lesions produce hemiballism, has been challenged. Instead, these findings imply that lesions within different anatomic regions may cause hemiballism and this has been attributed to the affection of basal ganglia circuits.

Diffusion MRI enables in vivo delineation of fiber pathways within the human brain. Advances in tractography algorithms have made it possible to identify white matter connections of different orientations, even in regions with a complex topography of pathways, such as the basal ganglia [6,7].

Abbreviations: DBS, Deep Brain Stimulation; GPe, globus pallidus externus; GPi, globus pallidus internus; LSD, least significant difference; M1, primary motor cortex; PMC, premotor cortex; S1, primary sensory cortex; SMA, supplementary motor area; SSMA, supplementary sensorimotor area; TMS, transcranial magnetic stimulation.

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The aim of this study is to explore the anatomic distribution of focal lesions inducing hemiballism and to study the neural circuits they affect with the aim of gaining a deeper understanding of basal ganglia physiology. We raise the hypothesis that hemiballism is caused by a dysbalance within the basal ganglia motor circuits rather than by an isolated lesion within one anatomic structure.

2. Materials and methods

2.1. Selection of patients and probands

Neurological and neuroradiological archives of our hospital from 1999–2013 were searched using the search string "hemiballism" and 'basal ganglia'. Initial search yielded 10467 hits. We excluded all patients without availability of CT/MRI scans and all patients with non-vascular lesions. Thus, 122 patients remained and their clinical reports were screened for symptoms of hemiballism and other clinical signs of stroke. To ensure a direct lesion-symptom correlation and pathogenetic causality, only patients with acute symptom onset and detection of a single corresponding focal vascular, i.e. ischemic or hemorrhagic, lesion were included. Any evidence of concomitant etiologies of hemiballism, paraneoplastic, infectious, hyperglykemic and motion artefacts were rated as exclusion criteria. Finally, eight patients with acute-onset hemiballism following a vascular lesion qualified for inclusion in this study. A clinical presentation of hemiballism is presented as supplementary material. The video was taken at the patient's presentation to our emergency ward, which was two weeks after symptom onset.

MRI scans including diffusion sequences were performed in 15 healthy, right-handed controls with a mean age of 30 years in order to establish a template of physiological basal ganglia connections. The rationale for selecting young probands was to better delineate pathways without having to deal with fiber restrictions that may arise with age.

Written informed consent was obtained from included patients and subjects. This study was approved of by the local ethics committee in accordance with the Declaration of Helsinki.

2.2. Data acquisition and diffusion data pre-processing

We obtained structural T1-weighted sequences (TE 3.2, TR 6.6, 180 slices, slice thickness 1.0, matrix 240×240, number of b0-images:1) and diffusion weighted images (b value 1000 s/mm^{-2}, 60 axial slices, slice thickness 2,4 mm, SENSE factor 2, 64 diffusion directions) on a 3-T MRI scanner (GE Signa Exite HD) from all controls. All image processing was carried out using the FSL software library (FSL 5.0.1 [8]; www.fmrib.ox.co.ac.uk). Diffusion data was pre-processed performing the following steps within the FSL toolbox: (1) eddy-current and head motion correction (2) brain extraction (3) fitting diffusion tensors on 4D data (4) fitting a probabilistic diffusion model (number of fibers per voxel: 3; burning period 1000, number of jumps 1250, sample every 25, model: sticks with a range of diffusivity) [9].

2.3. Data coregistration

Patients' MRI scans were co-registered to the probands' anatomic and diffusion scans. Initially, intra-individual datasets were co-registered applying a linear transformation (FSL: FLIRT; cost function: correlation ratio; degrees of freedom: 6; interpolation: trilinear); next, a non-linear transformation was applied (number of non-linear iterations = 5,5,5,5; sub-sampling = 4,2,1,1; lambda = 300,150,100,50).

Normalisation to standard space for group analysis was also performed with linear and non-linear transformations [8,9].

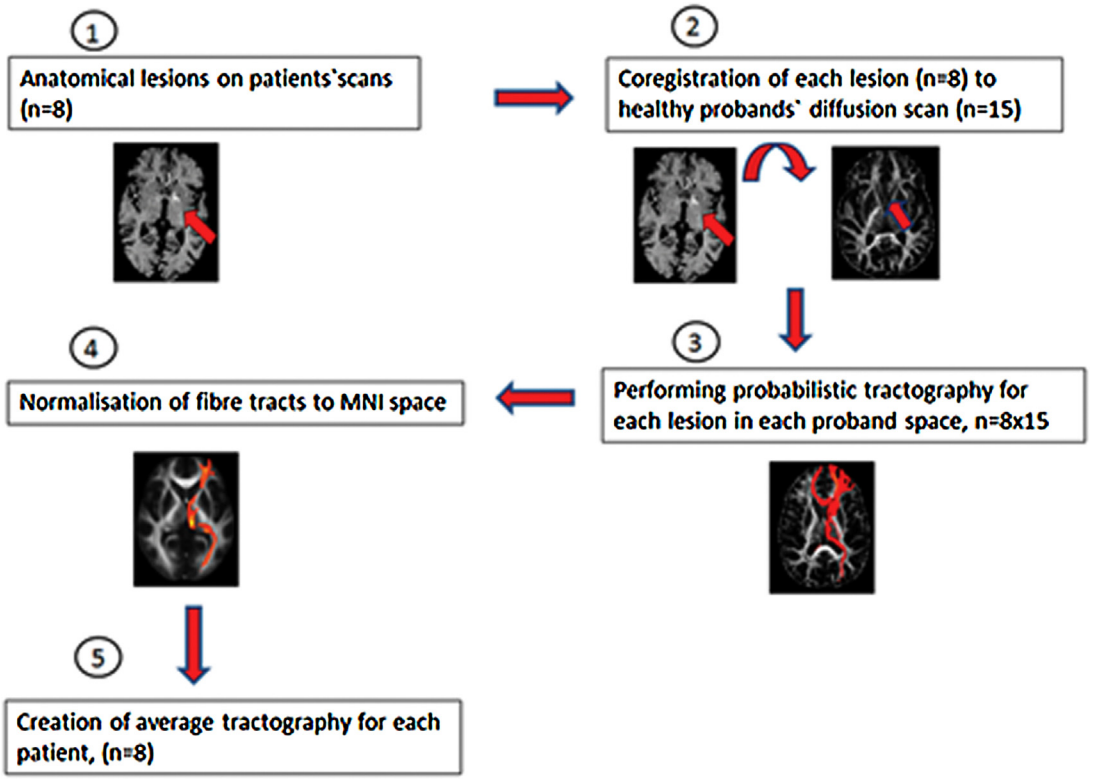

Fig 1. The figure displays the data pipeline followed in this study. Patients were selected (1), their lesions coregistered to healthy probands' scans (2) and probabilistic tractography initiated from these lesions (3). Resulting tracts were then averaged and normalised to MNI space (4).