NeuroImage: Clinical 18 (2018) 770–783

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

The anatomy of the human medial forebrain bundle: Ventral tegmental area connections to reward-associated subcortical and frontal lobe regions

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ARTICLE INFO

Keywords:
Brain
Deep brain stimulation
Depression
Human
Medial forebrain bundle
Normal anatomy
Obsessive compulsive disorder
TMS

ABSTRACT

Introduction: Despite their importance in reward, motivation, and learning there is only sparse anatomical knowledge about the human medial forebrain bundle (MFB) and the connectivity of the ventral tegmental area (VTA). A thorough anatomical and microstructural description of the reward related PFC/OFC regions and their connection to the VTA - the superolateral branch of the MFB (slMFB) - is however mandatory to enable an interpretation of distinct therapeutic effects from different interventional treatment modalities in neuropsychiatric disorders (DBS, TMS etc.). This work aims at a normative description of the human MFB (and more detailed the slMFB) anatomy with respect to distant prefrontal connections and microstructural features.

Methods and material: Healthy subjects (n = 55; mean age ± SD, 40 ± 10 years; 32 females) underwent high resolution anatomical magnetic resonance imaging including diffusion tensor imaging. Connectivity of the VTA and the resulting slMFB were investigated on the group level using a global tractography approach. The Desikan/Killiany parceling (8 segments) of the prefrontal cortex was used to describe sub-segments of the MFB. A qualitative overlap with Brodmann areas was additionally described. Additionally, a pure visual analysis was performed comparing local and global tracking approaches for their ability to fully visualize the slMFB.

Results: The MFB could be robustly described both in the present sample as well as in additional control analyses in data from the human connectome project. Most VTA- connections reached the superior frontal gyrus, the middel frontal gyrus and the lateral orbitofrontal region corresponding to Brodmann areas 10, 9, 8, 11, and 11m. The projections to these regions comprised 97% (right) and 98% (left) of the total relative fiber counts of the slMFB.

Discussion: The anatomical description of the human MFB shows far reaching connectivity of VTA to reward-related subcortical and cortical prefrontal regions - but not to emotion-related regions on the medial cortical surface - realized via the superolateral branch of the MFB. Local tractography approaches appear to be inferior in showing these far-reaching projections. Since these local approaches are typically used for surgical targeting of DBS procedures, the here established detailed map might - as a normative template - guide future efforts to target deep brain stimulation of the slMFB in depression and other disorders related to dysfunction of reward and reward-associated learning.

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https://doi.org/10.1016/j.nicl.2018.03.019
Received 18 January 2018; Received in revised form 13 March 2018; Accepted 14 March 2018
Available online 18 March 2018

We dedicate this work to Jaak Panksepp, Ph.D. (*1943 - †2017).

1. Introduction

The medial forebrain bundle (MFB) is an important structure for reward and motivation in the mammalian brain (Wise, 2005; Olds & Fobes, 1981; Zacharopoulos et al., 2016; Morgane & Panksepp, 1981; Panksepp, 1985; Alcaro et al., 2007) that also plays a central role in human affective disorders (e.g. depression, obsessive compulsive disorder) (Russo & Nestler, 2013; Döbrössy et al., 2015; Schlaepfer & Lieb, 2005) particularly for disease regulation (Coenen et al., 2011). The anatomy of the human medial forebrain bundle (MFB) was initially described in vivo in the context of psychotropic effects of deep brain stimulation (DBS) using diffusion tensor imaging and fiber tracking (Coenen et al., 2009). A detailed anatomical description revealed converging projections to the prefrontal cortex (PFC) shared with the anterior thalamic radiation (ATR) besides the expected subcortical connections to the ventral striatum (nucleus accumbens, NAC) which are reached over the anterior limb of the internal capsule (ALIC) (Coenen et al., 2012a). Similar findings were reported by others in part using different tractographic approaches modalities (Zacharopoulos et al., 2016; Bracht et al., 2014a; Bracht et al., 2014b; Bracht et al., 2015; Gálvez et al., 2014; Anthofer et al., 2015; Hana et al., 2015; Cho et al., 2015; Owens et al., 2016; Fenoy et al., 2016).

The clinical significance of the MFB for the treatment of affective disorders has only recently become evident (Coenen et al., 2011). For instance, Blood et al. found microstructural changes in the subcortical reward pathways of patients with major depression (Blood et al., 2010a). Bracht et al. observed distinct effects on the microstructure in a slMFB sub-segment which were associated with the melancholic depression phenotype. In this context microstructural slMFB changes were also reported with respect to anhedonia (Bracht et al., 2014a; Bracht et al., 2014b).

Furthermore, the superolateral branch of the MFB (slMFB) has been discovered as a target for DBS in treatment resistant depression (Coenen et al., 2011; Schlaepfer et al., 2014), bipolar disorder (Gippert et al., 2016), and obsessive compulsive (Coenen et al., 2016) disorder with encouraging in part long term results in small single center pilot series for depression (Fenoy et al., 2016; Schlaepfer et al., 2013; Bewernick et al., 2017).

However, choosing the slMFB as a possible target site for chronic DBS in depression (Fenoy et al., 2016; Schlaepfer et al., 2013) and OCD (Coenen et al., 2016) demands a more detailed knowledge about MFB anatomy per se and specifically about its projections to the PFC. In fact, DBS of other subcortical target regions (vc/vs = ventral capsule ventral striatum; cg25 = Brodman's area 25) for major depression has been shown to partly exert remote influence on prefrontal regions (Riva-Posse et al., 2017; Riva-Posse et al., 2014; Noecker et al., 2018) and their adjacent white matter (WM) tracts, especially the anterior prefrontal cortex (aPFC, BA10). The therapeutic overlap related to the PFC is interesting for the interpretation of results and therapeutic efficacy with respect to existing distinct disease phenotypes. Moreover, non-invasive therapies like electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) exert their therapeutic effects by possibly affecting very similar prefrontal regions (Cusin & Dougherty, 2012), opening the road for more personalized and focal interventions.

In this respect, possible microstructural differences of distinct slMFB segments in the diseased as opposed to a control population might be of interest in order to understand the antidepressant effects of any intervention in major depression. Bracht et al. have described a tripartite cortical segmentation of the slMFB projecting to lateral and medial orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (dlPFC) but without a clear anatomical and descriptive focus (Bracht et al., 2014a). Zacharopolus et al. applied dRL-tractography in conjunction with McDESPOT (Multi-Component Driven Equilibrium Single Pulse Observation of T1 and T2) and have looked at the slMFB as one of the hedonic hubs in the human brain (Zacharopoulos et al., 2016).

Although all these findings appear promising and important, the MFB parcellations used in these studies were not anatomically driven. Effective personalized and focal interventions however require detailed knowledge of the individual anatomy and microstructural pathology of fiber connections between reward-related subcortical and cortical structures.

Thus, with the growing interest in the effects of MFB alterations and its direct manipulation through DBS and other non-invasive stimulation technologies, the formal description of its structure in a common atlas space gains importance. To the best of our knowledge, besides an anatomical description that focuses mainly on subcortical structures (12), a detailed description of the anatomy of the MFB – and the slMFB - particularly with respect to PFC's reward associated regions in a normalized atlas space is as of yet not available.

Therefore, here we report the normative reconstruction of the MFB in a larger cohort of 55 normal controls using an advanced and state-of-the-art DTI-based fiber tracking algorithm (Reisert et al., 2011). The main objective was to anatomically depict the far reaching subcortico-cortical connections between the VTA and the PFC/OFC in a common atlas space (MNI 152 (Montreal Neurological Institute,Canada, Brain Template), 6th generation), by that describing detailed normal MFB anatomy. We further investigated microstructural features based on a new sub-segmentation of the slMFB that is derived from parceling the prefrontal cortex derived from the Desikan/Killiany atlas (Desikan et al., 2006) again using the global tracking approach. Note that the structure described and mainly scrutinized here is the superolateral branch of the MFB (slMFB). The concept of inferomedial (imMFB) – representing the phylogenetically older and lateral hypothalamic part, which is not in detail regarded here - and superolateral MFB - as the evolutionary younger and cortex connecting structure - in our eyes is still valid (Coenen et al., 2009; Coenen et al., 2012a).

2. Methods

2.1. Subjects

Healthy subjects (n = 55; mean age ± SD, 40 ± 10 years; 32 females) were recruited. The cohort presented here is part of a project that was reviewed by Freiburg University ethics committee (no. 528/15). Subjects were screened for depressive symptoms with the German version of the Beck's depression inventory (BDI-II; (Beck et al., 1996)) and excluded if their score was higher than 13 points, corresponding to the cutoff value for 'minimal or no depressivity'; The mean BDI-II score for depressivity was 3.8 (± 3.7), none of the subjects showed signs of depression.

2.2. Magnetic resonance imaging

Subjects were scanned on a Siemens 3 T TIM PRISMA using an SE EPI sequencewith a TE = 88 ms and TR = 2008 ms, bandwidth 1780 Hz, flip-angle 90°, GRAPPA factor 2, SMS factor 3 with 17 non-diffusion weighted images, 2*58 images with b-factor b = 1000 and 2000 s/mm^2; with an in-plane voxel size of 1.5 mm × 1.5 mm and a slice thickness of 3 mm. The overall sequence takes about 6 min of scan time. One phase-encoding flipped b = 0 image was acquired, which is used for distortion correction (FSL's top up (Andersson et al., 2003)). Additionally, a T1-weighted structural dataset was acquired, resolution 1 mm isotropic, TR = 2500 ms, TE = 2.82 ms.

2.3. Diffusion analysis and fiber tracking in subject space

The diffusion weighted images were first denoised by a post-processing technique which uses random matrix theory (see (Veraart et al., 2016) for details). This is followed by a Gibbs artifact removal (Kellner