CORTEX 84 (2016) 1–14

Available online at www.sciencedirect.com

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Journal homepage: www.elsevier.com/locate/cortex

Shared neural correlates of limb apraxia in early stages of Alzheimer's dementia and behavioural variant frontotemporal dementia

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ARTICLE INFO

Article history:
Received 21 December 2015
Reviewed 16 March 2016
Revised 7 May 2016
Accepted 6 August 2016
Action editor Stefano Cappa
Published online 26 August 2016

Keywords:
Limb apraxia
Voxel-based morphometry (VBM)
Behavioural variant frontotemporal dementia (bvFTD)
Alzheimer's dementia (AD)

ABSTRACT

Limb apraxia denotes a cognitive impairment of gesture production. Lesion studies in patients with stroke point towards distinct neural processing streams for limb imitation and object-pantomime within left parietal and temporal cortex, respectively. Despite its frequent occurrence as an early symptom in both, Alzheimer's dementia (AD) and behavioural variant frontotemporal dementia (bvFTD), neural correlates of limb apraxia within these patient groups remain unexplored. Using voxel-based morphometry and multiple regression models, associations between limb apraxia and gray matter (GM) volume were investigated in 36 dementia patients (18 AD, 18 bvFTD) in early disease stages. Both dementia subtypes showed a comparable degree of limb apraxia. Although the patient groups showed distinct atrophy patterns with significantly more severe frontal GM loss in bvFTD, we found similar neural correlates of limb apraxia within posterior brain regions for both dementia subtypes: limb-imitation was associated with bilateral atrophy of superior, inferior and medial parietal cortex. Object-pantomime showed associations with GM volume in right middle temporal and angular gyrus. Our results argue for shared neural correlates of limb apraxia in AD and bvFTD and validate the syndrome as an important neuropsychological feature across different etiologies. Moreover, our results are compatible with neural models derived from patients with stroke, suggesting partly distinct neural representations of imitation and pantomime. Compared to patients with stroke however, AD and bvFTD showed more bilateral or even right lateralized neural representations of limb apraxia, proposing a greater influence of visuospatial impairments and spatial body representation deficits on praxis performance.

1. Introduction

Limb apraxia describes a cognitive disorder that is defined by deficits in the ability to imitate gestures and pantomime the use of tools. These gestural deficits appear in the absence of sensory loss, muscular weakness, paresis or other low-level motor disorders and are a frequent consequence of left hemispheric stroke (Goldenberg, 2009; Gonzalez Rothi,

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http://dx.doi.org/10.1016/j.cortex.2016.08.009
0010-9452/

Ochipa, & Heilman, 1991). Voxel-based lesion-symptom mapping (VLSM) approaches have only recently enabled more elaborated empirical investigations of the neural correlates of praxis disturbances in patients with stroke (Buxbaum, Shapiro, & Coslett, 2014; Goldenberg & Randerath, 2015; Hoeren et al., 2014; Manuel et al., 2013; Niessen, Fink, & Weiss, 2014; Vry et al., 2014). Results from these lesion studies are currently interpreted using diverse adaptations of an influential model of action perception (Goodale & Milner, 1992; Milner & Goodale, 2008). One recently proposed model for "gesture production" constitutes three essentially separated neural "pathways" subserving different functions of praxis (Binkofski & Buxbaum, 2013; Hoeren et al., 2014). All three pathways are assumed to originate in early visual regions within the occipital lobe, and then either stretch into medial and superior parietal (dorso-dorsal stream), inferior parietal (ventro-dorsal stream) or temporal (ventral stream) cortical areas (Binkofski & Buxbaum, 2013; Hoeren et al., 2014; Vry et al., 2014). The functional role of the ventral stream has been described as critical for object identification and retrieval of action- or object-related information from semantic memory, thus mainly contributing to pantomime of object-use and other communicative gestures (Brandi, Wohlschläger, Sorg, & Hermsdörfer, 2014; Goldenberg & Randerath, 2015; Martin et al., 2015; Tyler et al., 2013). The ventro-dorsal stream (with its core region inferior parietal lobe, IPL), has originally been conceptualized to be crucial for access to stored "action engrams", i.e., representations of skilled gestures and actions within long-term storage (Binkofski & Buxbaum, 2013) but some authors also stress its role in structural posture analysis for imitation (e.g., Goldenberg, 2009). Recent VLSM studies have shown a role of IPL for both pantomime of object-use and imitation of meaningless gestures to different degrees (Buxbaum et al., 2014; Goldenberg & Randerath, 2015; Hoeren et al., 2014). Finally, the dorso-dorsal stream is supposed to be essential for online sensorimotor adjustments e.g., needed for grasping of objects. Lesions within the core area of this stream, the superior parietal lobe (SPL), can lead to misreaching and optic ataxia (Karnath & Perenin, 2005). Recently however, the functional role of the dorso-dorsal stream has been extended to also include online representations of body-parts during imitation of spatially complex meaningless postures and for converting these spatial representations into motor commands (Hoeren et al., 2014). In summary, although the involvement of the different streams in praxis functions are controversially discussed regarding details, current data suggests more ventral (temporal and inferior parietal) involvement for semantically meaningful gestures (e.g., pantomime of object-use and meaningful imitation) and more dorsal (superior and inferior parietal) involvement for the imitation of meaningless gestures.

Apart from patients with stroke, limb apraxia has also been described as a common symptom in early stages of several neurodegenerative diseases including Alzheimer's dementia (AD) and behavioural variant frontotemporal dementia (bvFTD) (Crutch, Rossor, & Warrington, 2007; Johnen, Frommeyer, et al., 2015; Johnen, Tokaj, et al., 2015; Lesourd et al., 2013; Rousseaux, Rénier, Anicet, Pasquier, & Mackowiak-Cordoliani, 2012). Despite its potential as an early and validly assessable cognitive feature, apraxia is currently underrepresented in both-clinical research and diagnostic guidelines for these dementia syndromes (McKhann et al., 2011; Rascovsky et al., 2011). Due to lacking brain imaging data, it is moreover unclear (1) which brain areas contribute to limb apraxia in AD or bvFTD, (2) whether AD and bvFTD have common neural substrates underlying limb apraxia and (3) whether these areas overlap with existing data from patients with stroke regarding limb imitation and pantomime. As lesions are usually more widespread in neurodegenerative diseases, associations between cognitive deficits and brain atrophy may differ from patients with focused lesions from e.g., stroke or tumor. Converging neural substrates of limb apraxia in patients with such different etiologies may on the other hand validate current concepts and definitions of the syndrome and its proposed neural representations. With the current study, we aim to explore neural substrates of limb imitation and pantomime of object-use in patients with AD and bvFTD in early disease stages, using a high-dimensional voxel-based morphometry (VBM) approach. We will relate our findings to the presented stream model for gesture production deduced from stroke research.

2. Materials and methods

2.1. *Participants*

Patients were recruited from the memory disorder unit at the Department of Neurology of the University Hospital Münster, Germany, between June 2013 and August 2015. All participants gave written informed consent. The study was approved by the local ethic committee (2012-365-f-S). Initial diagnoses were made by a multidisciplinary team of trained clinicians according to current clinical criteria of AD and bvFTD respectively (McKhann et al., 2011; Rascovsky et al., 2011). Patients with AD ($N = 18$) presented with typical clinical pictures of early progressive memory impairments, whereas bvFTD patients ($N = 18$) exhibited prominent changes in personality and social conduct as confirmed by relatives or caregivers. Behavioural deterioration was validated by the Frontal Behavioural Inventory (FBI; Kertesz, Davidson, & Fox, 1997), a standardized caregiver interview. As part of standard diagnostic workup, all patients received detailed neurological examination and history taking, neuropsychological assessment and MRI scans of the brain at 3.0 T at initial presentation. In case MRI scans did not reveal unambiguous results regarding focal atrophy patterns, a subsample of patients additionally received an 18-fluorodeoxyglucose PET scan to detect regional brain hypometabolism (4/18 AD, 15/18 bvFTD). Patient's cerebrospinal fluids (CSF) were analyzed for potential inflammation and for dementia CSF biomarkers (total tau-protein and amyloid-β peptide level). Disease duration was assessed by interviewing caregivers and by consulting clinical records. All patients had at least one follow-up diagnostic consultation within eight months after initial presentation before study inclusion, in order to validate the diagnosis through the documentation of cognitive and/or behavioural decline (e.g., in order to prevent the inclusion of so-called "phenocopy type" bvFTD patients; Kipps, Hodges, & Hornberger, 2010; Gossink et al. 2015). If