NeuroImage: Clinical 5 (2014) 217–231

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Review

Neuroimaging essentials in essential tremor: A systematic review

Sarvi Sharifi[a,b], Aart J. Nederveen[b,c], Jan Booij[b,d], Anne-Fleur van Rootselaar[a,b,*]

[a]Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands
[b]Brain Imaging Center, Academic Medical Center, Amsterdam, The Netherlands
[c]Department of Radiology, Academic Medical Center, Amsterdam, The Netherlands
[d]Department of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 16 January 2014
Received in revised form 3 May 2014
Accepted 5 May 2014
Available online 9 May 2014

Keywords:
Essential tremor
Neuroimaging
Review
MRI
Scintigraphy
Pathophysiology

ABSTRACT

Background: Essential tremor is regarded to be a disease of the central nervous system. Neuroimaging is a rapidly growing field with potential benefits to both diagnostics and research. The exact role of imaging techniques with respect to essential tremor in research and clinical practice is not clear. A systematic review of the different imaging techniques in essential tremor is lacking in the literature.
Methods: We performed a systematic literature search combining the terms essential tremor and familial tremor with the following keywords: imaging, MRI, VBM, DWI, fMRI, PET and SPECT, both in abbreviated form as well as in full form. We summarize and discuss the quality and the external validity of each study and place the results in the context of existing knowledge regarding the pathophysiology of essential tremor.
Results: A total of 48 neuroimaging studies met our search criteria, roughly divided into 19 structural and 29 functional and metabolic studies. The quality of the studies varied, especially concerning inclusion criteria. Functional imaging studies indicated cerebellar hyperactivity during rest and during tremor. The studies also pointed to the involvement of the thalamus, the inferior olive and the red nucleus. Structural studies showed less consistent results.
Discussion and conclusion: Neuroimaging techniques in essential tremor give insight into the pathophysiology of essential tremor indicating the involvement of the cerebellum as the most consistent finding. GABAergic dysfunction might be a major premise in the pathophysiological hypotheses. Inconsistencies between studies can be partly explained by the inclusion of heterogeneous patient groups. Improvement of scientific research requires more stringent inclusion criteria and application of advanced analysis techniques. Also, the use of multimodal neuroimaging techniques is a promising development in movement disorders research. Currently, the role of imaging techniques in essential tremor in daily clinical practice is limited.

Contents

Abbreviations: MRI, magnetic resonance imaging; VBM, voxel-based morphometry; DWI, diffusion weighted imaging; fMRI, functional magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

* Corresponding author at: Department of Clinical Neurophysiology D2-113, Academic Medical Center, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands.
E-mail address: A.f.vanrootselaar@amc.uva.nl (A.-F. van Rootselaar).

http://dx.doi.org/10.1016/j.nicl.2014.05.003

1. Introduction

Amongst the movement disorders, essential tremor is one of the most prevalent disorders. Up to 5% of individuals above the age of 65 years are coping with essential tremor (Louis and Ferreira, 2010). Clinical diagnostic criteria have been developed over the years. The exact clinical definition of essential tremor is however still under debate. Current clinical diagnosis based on the consensus statement of the Movement Disorder Society typically has an estimated error margin of 37% of false-positives (Jain et al., 2006). Neuroimaging techniques could potentially lower the margin of error in diagnostics by gaining insight into underlying brain pathology and could ultimately be used as a valid diagnostic tool.

The pathophysiology of essential tremor is only partially understood. Thus far, surgical, post-mortem, neurophysiological and animal studies point to the involvement of the inferior olive, the cerebellum, the red nucleus, the thalamus, the cortex and their neurotransmitter systems. These areas make up a network known as the cerebello-thalamo-cortical network or tremor network (Fig. 1) (Hallett, 2014). Olivary afferents travel through the inferior cerebellar peduncle to end in cerebellar nuclei or form synapses with GABAergic inhibitory Purkinje cells in the cerebellar cortex. Purkinje cells send inhibitory projections to the deep cerebellar nuclei including the dentate nucleus. Cerebellar nuclei project via the thalamus to the cerebral cortex, yet other projections end in the red nucleus. The exact mechanisms and possible structural or functional changes within the tremor network are not fully understood. There is an ongoing debate whether essential tremor is primarily (1) a neurodegenerative disorder with actual progressive cell loss, (2) a disorder with localized GABAergic dysfunction, or (3) a disorder caused by abnormal neuronal oscillations within the tremor network (Bonuccelli, 2012; Deuschl and Elble, 2009; Helmich et al., 2013; Louis, 2009; Rajput et al., 2012a). These hypotheses are not mutually exclusive per se. Neuroimaging techniques might give insight into these three and even other concepts concerning the pathophysiology of essential tremor. Neuroimaging is a rapidly developing field. A variety of imaging studies have been performed in essential tremor patients over the past decade. Our aim is to systematically review these neuroimaging studies in essential tremor and discuss the pathophysiology of essential tremor from a neuroimaging perspective.

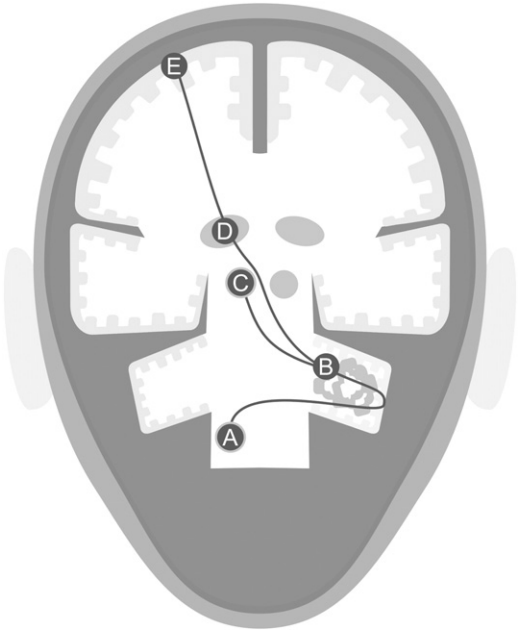

Fig. 1. Tremor network: A) inferior olive; B) dentate nucleus; C) red nucleus; D) thalamus; E) motor cortex.

2. Methods

We queried the OvidSP Embase Classic+Embase and the Ovid MEDLINE® In-Process & Other Non-Indexed Citations from January 1st, 1947 to August 5th, 2013 using the terms 'essential tremor' and 'familial tremor' (Appendix A) in combination with the imaging keywords and their abbreviations stated in Table 1.

Only original English-written articles that recruited both essential tremor patients and healthy controls were included. We identified brain regions and networks associated with essential tremor. Our main research questions for our systematic search were as follows: (1) are results of imaging studies congruent with areas within the known tremor network and valid in the scope of their imaging technique? (2) do the imaging studies help better understand the different hypotheses on the pathophysiology (neurodegeneration, GABA, oscillating network)? and (3) what recommendations can be set for future imaging research arising from current literature?

3. Results

A total of 375 abstracts of imaging studies were identified. We excluded abstracts in case they did not address a neuroimaging technique of interest or had deep brain stimulation as main topic. We also excluded studies that did not include patients with postural tremor and studies without a group of healthy controls. A total of 48 imaging studies met our inclusion criteria which account for a total of 713 essential tremor patients divided over 19 structural studies and 29 functional and receptor imaging studies (Fig. 2). Structural techniques include volumetry, white matter diffusion imaging, magnetic resonance spectroscopy, T2-FLAIR and T2*-relaxometry. Functional and molecular imaging methods include perfusion, glucose metabolism and receptor imaging.

3.1. Structural imaging in essential tremor

Structural MRI, as used in current clinical practice, does not reveal significant abnormalities in individual essential tremor patients. Pathological studies however do indicate structural changes (Louis, 2010). More advanced imaging techniques in (sub)groups of patients might

Table 1
Keywords and abbreviations used in the literature search

Keyword	Abbreviation
Magnetic Resonance Imaging	MRI
Voxel-Based Morphometry	VBM
Diffusion Weighted Imaging	DWI
Functional Magnetic Resonance Imaging	fMRI
Positron Emission Tomography	PET
Single-Photon Emission Computed Tomography	SPECT
Magnetic Resonance	-
Tomography	-
Scintigraphic Imaging	-