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Structural connectivity differences in left and right temporal lobe epilepsy

Pierre Besson [a,b,1], Vera Dinkelacker [c,d,e,*,1], Romain Valabregue [d,e], Lionel Thivard [e], Xavier Leclerc [b], Michel Baulac [c,e], Daniela Sammler [d,f], Olivier Colliot [e,g], Stéphane Lehéricy [d,e], Séverine Samson [c,h], Sophie Dupont [c,d,e]

[a] Department of clinical neurophysiology EA 1048, Lille University Hospital, France
[b] In-vivo Imaging Platform, IMPRT, Lille University Hospital, France
[c] Epilepsy Unit, Hôpital de la Pitié-Salpêtrière, APHP, Paris, France
[d] Centre de Neuroimagerie de Recherche (CENIR), Paris, France
[e] Centre de Recherche de l'Institut du Cerveau et de la Moëlle Epinière (ICM), Université Pierre et Marie Curie Paris 6 – UMR 7225 CNRS – UMR-S975 INSERM, Paris, France
[f] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[g] INRIA, Aramis Team, Centre de Recherche Paris-Rocquencourt, France
[h] Laboratoire de Neurosciences Fonctionnelles et Pathologies (EA 4559), Université Lille-Nord de France, France

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ABSTRACT

Our knowledge on temporal lobe epilepsy (TLE) with hippocampal sclerosis has evolved towards the view that this syndrome affects widespread brain networks. Diffusion weighted imaging studies have shown alterations of large white matter tracts, most notably in left temporal lobe epilepsy, but the degree of altered connections between cortical and subcortical structures remains to be clarified. We performed a whole brain connectome analysis in 39 patients with refractory temporal lobe epilepsy and unilateral hippocampal sclerosis (20 right and 19 left) and 28 healthy subjects. We performed whole-brain probabilistic fiber tracking using MRtrix and segmented 164 cortical and subcortical structures with Freesurfer. Individual structural connectivity graphs based on these 164 nodes were computed by mapping the mean fractional anisotropy (FA) onto each tract. Connectomes were then compared using two complementary methods: permutation tests for pair-wise connections and Network Based Statistics to probe for differences in large network components. Comparison of pair-wise connections revealed a marked reduction of connectivity between left TLE patients and controls, which was strongly lateralized to the ipsilateral temporal lobe. Specifically, infero-lateral cortex and temporal pole were strongly affected, and so was the perisylvian cortex. In contrast, for right TLE, focal connectivity loss was much less pronounced and restricted to bilateral limbic structures and right temporal cortex. Analysis of large network components revealed furthermore that both left and right hippocampal sclerosis affected diffuse global and interhemispheric connectivity. Thus, left temporal lobe epilepsy was associated with a much more pronounced pattern of reduced FA, that included major landmarks of perisylvian language circuitry. These distinct patterns of connectivity associated with unilateral hippocampal sclerosis show how a focal pathology influences global network architecture, and how left or right-sided lesions may have differential and specific impacts on cerebral connectivity.

Introduction

Temporal lobe epilepsy (TLE) with hippocampal sclerosis (HS) has for a long time been perceived as a focal disease centered on a single lesion. Epilepsy surgery showed that seizures originate in an epileptic hippocampus, and can be suppressed by resection of this epileptic focus (Dupont et al., 2006; Wieser et al., 2003). Pioneering work on hippocampal function detected early on that the lateralization of the disease had differential impact on cognition, the left sided temporal lesions being associated with deficits in verbal memory, the right sided in non verbal memory (Frisk and Milner, 1990; Milner, 1972; Smith and Milner, 1989). However, neuropsychological curtailing in brain regions at distance of the hippocampus were not explained by this lesion centered vision (Stretton and Thompson, 2012).

Our view on TLE has much evolved with the advent of neuroimaging techniques yielding ample data on TLE as a network disease. Whereas positron-emission-tomography studies pointed out extra-hippocampal

* Corresponding author at: Hôpital Pitié-Salpêtrière, Neurophysiologie, 47 - 83 blvd de l'Hôpital, 75013 Paris, France.
E-mail address: v.dinkelacker@gmail.com (V. Dinkelacker).
[1] These two authors contributed equally to this work.

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dysfunction of the temporal pole and the frontal lobes (Dupont et al., 2002; Jokeit et al., 1997; Semah et al., 1995), voxel based morphometry was the initial cornerstone for quantitative analysis of extra-temporal curtailing (Bernasconi et al., 2004; Bonilha et al., 2007; Keller et al., 2002).

Instead of assessing changes in gray matter volume or metabolism, diffusion weighted imaging (DWI) is best suited to disentangle white matter abnormalities. Seminal DWI studies confirmed the presence of altered DWI signal beyond the diseased hippocampus, most notably contralateral to the seizure focus (Concha et al., 2005; Thivard et al., 2005b). In the following, different approaches of DWI methodology have been undertaken. First, large white matter bundles can be 'dissected' and compared between patients and control subjects. The integrity of parts of this gross white matter skeleton can then be correlated with neuropsychological measures (Diehl et al., 2008; McDonald et al., 2008; Yogarajah et al., 2008), thus establishing the link with the clinical picture of TLE. Of particular interest in terms of network pathology are here the deficits in 'extratemporal' tasks, as for example naming and verbal fluency, which correlated with the fractional anisotropy (FA) of arcuate fasciculus (Diehl et al., 2008; Kucukboyaci et al., 2012; McDonald et al., 2008; Yogarajah et al., 2008). Second, tractography from seed regions can be performed to assess hippocampal deafferentation (Bonilha et al., 2010) or language circuitry (Powell et al., 2008), and thus single out the individual connection pattern of a given region. Third, scrutiny of the entire brain circuitry (the 'connectome') can be performed, based either on the number of tractography streamlines or on the FA in order to assess the global network integrity (Bernhardt et al., 2011; Bonilha et al., 2012; Zalesky et al., 2010). The latter approach is the DWI based equivalent of morphological (Bernhardt et al., 2008) or functional imaging studies (Bernhardt et al., 2013; Bettus et al., 2008; Engel et al., 2013; Haneef et al., 2014; Richardson, 2013; Vlooswijk et al., 2010) on global alterations of brain circuitry. Its major advantage compared to the latter is the high resolution of structural white matter architecture, which sustains both cognitive information flow and seizure propagation (Gross, 2011).

Connectome analysis has gained much recent interest as a formal framework of quantitative network analysis. In graph theory, connections are termed *edges* and anatomical regions form *nodes* of a network enabling a mathematical analysis of the efficacy of information flow between distant nodes (Bonilha et al., 2012). In this framework, high clustering coefficients and relatively few long path connections ('small world') favor specialization and integration (Sporns and Zwi, 2004) and may correspond to a physiological brain circuitry pattern (Bernhardt et al., 2011). However, DWI based connectomics rely heavily on correct tractography at the gray and white matter interface and thus at the limits of the diffusion based signal to noise ratio (Jones et al., 2013). Furthermore, pathological interpretation has to be given with caution as DWI weighted measures such as FA may well be correlated with cerebral microstructure but will still reflect a mixture of diffusion effects such as myelin changes, axonal fiber loss or simply crossing fibers (Gross, 2011; Jeurissen et al., 2013).

Given all these considerations, what is our current understanding of network disease in TLE? Two major findings emerged from this large body of literature: on the one hand, alterations in DWI signal seem to be maximal at the epileptic zone and subtle at distance (Concha et al., 2012; Otte et al., 2012). On the other hand, 'side matters' as left TLE is apparently more affected than right (Ahmadi et al., 2009).

With respect to the epileptic zone, there appears to be a gradient effect of most pronounced, focal alterations in the diseased temporal lobe and the brain regions most connected to it, and progressively lesser effects at distance ((Bernhardt et al., 2011; Bettus et al., 2008, 2009; Bonilha et al., 2010), for a recent meta-analysis see Otte et al., 2012). This effect is readily explained by the atrophic hippocampal lesion and the excitotoxicity of seizure spread. It has been demonstrated both in regions of interest analysis of DWI imaging (Otte et al., 2012), in EEG (Bettus et al., 2008) and fMRI (Bettus et al., 2009) studies as in the first reports of alterations in graph characteristics related to TLE (Bonilha et al., 2012).

In terms of lateralization, left and right temporal lobe epilepsy seem to show a different pattern of network disease. Over the spectrum of imaging techniques, the majority of studies converge to the finding that left hemispheric disease has stronger impact on network function. This lateralization effect was shown for in large white matter bundles (Ahmadi et al., 2009; Kemmotsu et al., 2011), for voxel based morphometry of the cortical mantle (Bonilha et al., 2007; Riederer et al., 2008), FA in gray matter regions (Coan et al., 2009; Keller et al., 2012), and in resting state functional MRI (Haneef et al., 2014).

DWI differences between left and right sided disease are not easily assessed, they require a large number of patients to increase statistical power and a sufficient signal to noise ratio which is a delicate question in patient studies based on clinical DWI (Jones et al., 2013). This may explain why, to our knowledge, a direct comparison of the connectome in left and right sided TLE is still pending.

Differences in network pathology as a function of disease lateralization is a very intriguing finding, and of particular interest in the group of TLE with hippocampal sclerosis, as all patients have virtually the same lesion in the same brain area - only the side matters. Here, it is less intuitive to explain the differences with the disease mechanism, as it is the same in both patient groups. The lateralization effect might therefore emanate from the physiological network affected, and hence ultimately relate to different wiring of the dominant and non dominant hemisphere.

Our study intended to further explore both of these major findings – the gradient between local and distant connectivity alterations and the differences between left and right TLE. We felt that a global white matter connectome analysis would best suited to render a detailed topography of network pathology. For this purpose, we performed DWI recordings in a large and homogenous group of patients with temporal lobe epilepsy associated with unilateral left or right hippocampal sclerosis (39 patients and 28 healthy participants). We chose two complementary state of the art analysis strategies to capture both local and large scale changes in these syndromes: pair-wise connection comparisons yielding high local power and network-based statistics (Zalesky et al., 2010), which has been developed to probe interconnected network components. Combination of these two approaches should be suitable to disentangle not only local connectivity alterations adjacent to the sclerotic hippocampus but also the diffuse impact on interhemispheric circuitry. In line with prior findings of enhanced alterations of the gross white matter skeleton in left TLE, we anticipated to find large scale alterations of distal connectivity in the dominant hemisphere. In general terms, we intended to disentangle how a focal lesion can have differential impact on global circuitry depending on the side of the lesion.

Materials and methods

Patients and control subjects

We included in this study 39 consecutive patients with medically intractable TLE associated with unilateral hippocampal sclerosis. They all underwent presurgical evaluation in the epilepsy unit of the Pitié-Salpêtrière Hospital between 2007 and 2011. Twenty patients had right TLE (mean age = 39.3 ± 9.4 years; 11 were female, 2 were left-handed) and 19 left TLE (mean age = 39.8 ± 10.8; 10 female, one ambidextrous and one left-handed patient). Clinical diagnosis of hippocampal sclerosis was based on the presence of both unilateral hippocampal atrophy on high resolution T1-weighted and enhanced signal intensities in fluid-attenuated inversion recovery (FLAIR) images obtained with a 3 T MRI scanner. Diagnosis was confirmed by post-operative histopathologic exams in 22 patients of the 25 who had undergone surgery. Interictal and ictal scalp EEG confirmed unilateral seizure origin and post-surgical outcome was excellent (see supplementary data). In a

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