Project title

Early diagnosis of CJD from in vivo MRI using the trajectories of prion lesion propagation

Principal Investigator

Alberto Bizzi, MD

Neuroradiology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

Project synopsis

Clinical signs at onset and early pathogenic events vary with the subtype of sporadic CJD (sCJD). Successful therapeutics of sCJD will likely depend on early and accurate diagnosis and may need to be tailored to the prion disease subtype. Moreover, the knowledge of the subtype has implications for prognosis and patient's survival. Currently, the definite subtype is determined only at autopsy by neuropathological examination.

The aim of this study was to improve the early diagnosis of sCJD and of its subtypes by identifying the early signs of the disease on diffusion MR images and how they propagate in the brain. This was accomplished by using a data-driven method (named "Subtype and Stage Inference", or simply "SuStaIn") based only on diffusion MRI data to establish how many groups of patients with distinct trajectories of propagation could be identified in patients with sCJD. In a nutshell, SuStaIn determined these groups by identifying the most likely distinct trajectories followed by the prion to propagate within the brain. SuStaIn was developed for Alzheimer's disease and successfully applied to other neurodegenerative diseases, but this is the first time that it has been tested on sCJD.

Next, we aimed to correlate the groups identified by SuStaIn with the sCJD subtypes identified at autopsy by neuropathological examinations.

A third aim of this study was to investigate whether the sensitivities of other commonly used diagnostic cerebrospinal fluid tests (i.e., RT-QuIC, 14-3-3, and total tau) vary among the SuStaIn groups.

A fourth aim was to investigate with MR diffusion tractography whether the trajectories of prion lesion propagation identified by SuStain may be explained by the main white matter tracts that connect the involved brain regions, or whether other mechanisms of propagation should be considered.

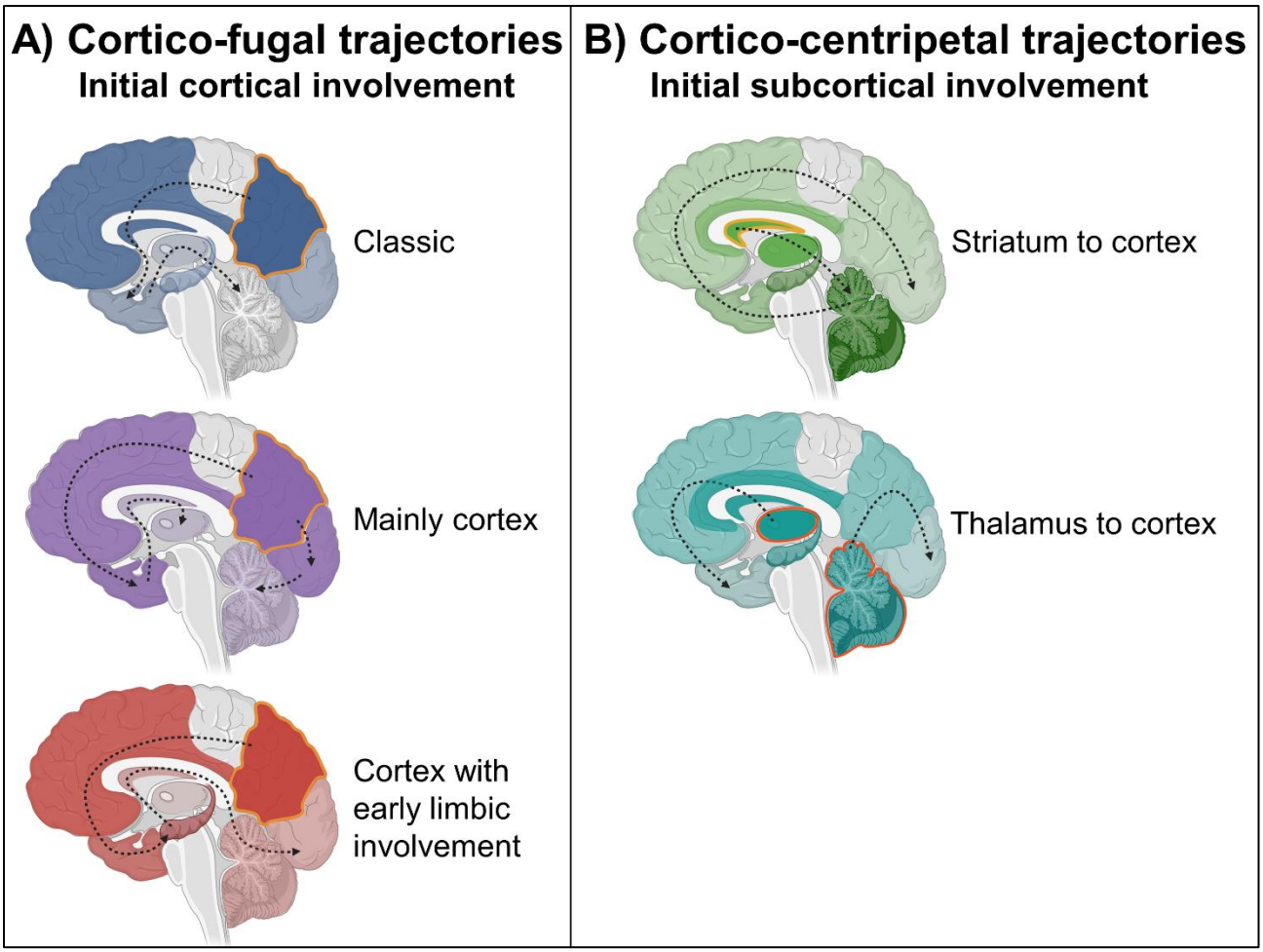
Project objectives

1) to identify the trajectories of lesion propagation in sCJD within the brain, based only on MRI.
2) to group sCJD patients with similar trajectories of propagation and correlate these groups with the sCJD autopsy-confirmed subtype. These MRI-defined groups would allow to determine the disease stage and to predict the disease evolution of any new patient.
3) to determine the sensitivity of three cerebrospinal fluid diagnostic tests (RT-QuIC, 14-3-3, and tau) for each SuStaIn group and compare them among the MRI groups.
4) to investigate the mechanism underpinning the propagation of prion diseases in the brain. With the aid of a diffusion MR tractography digital atlas we tested whether the propagation of prion lesions along the trajectories obtained with SuStain follow major white matter tracts that connect the affected brain regions.

Summary of accomplishments to date

Brain MRIs of 521 autopsy-confirmed sCJD patients were examined by one neuroradiologist who assigned a score of involvement to 12 brain regions. Based on the scores extracted from the imaging data, SuStaIn identified 5 distinct trajectories of lesion propagation: three showed an initial cortical involvement (Figure 1A); the epicenter of the other two trajectories was in subcortical structures (i.e., striatum and thalamus) and the cortex was involved only later (Figure 1B). The corticofugal trajectories were associated to patients with a prevalence of MM(MV)1, MM(MV)2C, and VV1 subtypes. The corticocentripetal trajectories were associated to patients with VV2 and MV2K subtypes.

Figure 1. Trajectories of lesion propagation identified by SuStaIn.



Note: the arrows indicate the trajectory of lesion propagation within the brain, according to the SuStaIn algorithm. The region with an orange border is the starting point (or "epicenter") of the trajectory. The subsequent affected regions on the trajectory are shown with progressively less intense colors. (A) Three trejectories with initial cortical involvement (in the parietal lobe). (B) Two trajectories with initial subcortical involvement (in the striatum and in the thalamus).

In detail, the three groups respectively associated to the three trajectories with initial cortical involvement were:

1) "Classic", the "epicenter" of the most common trajectory was found in the parietal lobe followed by an involvement of the frontal and temporal cortices and a relatively early involvement of the striatum. Coherently, this group mostly comprised patients with MM1 (79% 82/104), the most common sCJD subtype.
2) "Mainly cortex", the "epicenter" again was in the parietal cortex. Then the trajectory spread to all other cortical regions before it reached subcortical structures, which were affected quite late and only in a minority of patients. Most of the patients with MM(MV)2C subtype (about 73%, 62/85) were assigned to this group.

3) "Cortex with early limbic involvement", the epicenter was again in the parietal cortex. Then the trajectory spread to limbic regions and to the cortex of other lobes. The disease involved subcortical structures only late and only in a minority of patients assigned to this group. Most of the patients with VV1 subtype (about 57%, 16/28) were classified in this group.

The two groups with early subcortical involvement were:

1) "Striatum to cortex", with a trajectory characterized by an early involvement of the striatum, followed by thalamus and cerebellum and, only at a later time, by limbic and cortical regions. Most of the VV2 and MV2K patients (92/133, 69%) were assigned by SuStain to this group.
2) "Thalamus to cortex", with a trajectory characterized by an early involvement of the thalamus and cerebellum, followed by the striatum, the limbic regions, and the cortex at a very late stage. Almost all the VV2 and MV2K patients who were not assigned to the "Striatum to cortex" group (25/133, 19%) were classified in this group.

We investigated whether the sensitivies of three main cerebrospinal fluid diagnostic tests (RT-QuIC, total tau, and 14-3-3) were different among the five SuStaIn groups. The highest sensitivity for the RT-QuIC test was found in the "Classic" group (89%) and the lowest in the "Cortex with early limbic involvement" (68%) and "Mainly cortex" groups (79%). The highest sensitivity of the 14-3-3 test was also found in the "Classic" group (97% vs an average of 92% among all groups). The lowest sensitivity of this test was found in the "Mainly cortex" group (83%). In contrast, the highest sensitivity of the tau test was found in the "Striatum to cortex" group (95% vs an average of 87% among all groups); the lowest was found in the "Mainly cortex" group (78%).

To address the last aim of this project, we simulated the spread of prion pathology within the brain on a network composed of nodes (brain regions) and links between nodes (neural connections). We simulated the propagation starting from each of the "epicenters" of the previous 5 groups identified by SuStaIn. The simulated propagation followed the anatomical connections until all regions became affected. This experiment produced distinct simulated trajectories for each of the three epicenters (i.e., parietal cortex, caudate and thalamus), which were then compared with the SuStaIn trajectories. A good match was found only for the "Mainly cortex" and "Cortex with early limbic" groups, meaning that for those two groups the mechanism of lesion propagation is likely to follow major anatomical connections among brain regions. In contrast, no match was found for the other groups.

Mechanisms of disease propagation other than that following main white matter connections may be at play for the other three SuStain groups and they will be tested in a future study.

Key findings and implications for the prion disease field

We developed a powerful tool to identify sCJD patients with similar MRI features. Knowledge of the trajectory of lesion spreading will inform patient management and prognosis and may also have important benefits for prion disease surveillance. The identification of different possible "epicenters" of the disease in the brain, even within the same subtype, may facilitate an earlier diagnosis. The SuStain algorithm has potential to be used for early selection of sCJD patients and for stratifying them into arms of future clinical trials.

Manuscripts published and in preparation supported by this CJD Foundation Grant

- Venkatraghavan V, Pascuzzo R, Bron EE, … Bizzi A. (2023) A discriminative event-based model for subtype diagnosis of sporadic Creutzfeldt-Jakob disease using brain MRI. *Alzheimer's & Dementia*. doi: 10.1002/alz.12939 [In press]
- Pascuzzo R, Young AL, Oxtoby NP, …, Bizzi A. (2023) Distinct trajectories of lesion propagation in sporadic Creutzfeldt-Jakob disease revealed by Subtype and Stage Inference model from diffusion Magnetic Resonance Imaging. [In preparation]

Next steps

- Development of an automatic pipeline of analysis of brain MRI based on artificial intelligence algorithms that could support the radiologist in the diagnosis of sCJD and in the identification of the most affected brain regions directly on the image.
- Investigation of other propagation mechanisms: for instance, future studies will have to establish whether the more a brain region is connected to the others, the earlier it is affected.