Can stability of visual fixation be a measure for disability in multiple sclerosis?

Is there still room for discovery of novel clinical signs in patients with multiple sclerosis (MS)? The last century saw the Babinski sign indicating pathology to the central nervous system (CNS). It can be criticized for many reasons, but stood the test of time. Symptoms and signs in the visual system of patients with MS include internuclear ophthalmoplegia (INO), pendular nystagmus, Bielschowsky phenomenon, Pulfrich phenomenon, Uthoff phenomenon, the Marcus Gunn pupil, dyschromatopsia, poor contrast vision with relative preserved high contrast acuities, accelerated visual fading, any type of visual field defects with typically sloping borders of their isopters, and patterns of retinal layer thickness changes. The list seems exhaustive, but the group from UCSF presents a paper which implies that characteristics of microsaccades may eventually be added.

What are microsaccades? One of the phenomena listed above is a well known party trick, visual fading. If the reader draws a small dot on a paper and rigorously, constantly fixes this point with one eye while the other is closed (constantly fixating is the key), then the point will fade away. In spite of the knowledge of the point existing, it is impossible to see it anymore. Look away and look back, you will see it again. This is one of the 'raisons d'etre' for microsaccades, to prevent neural adaptation that would result in visual fading. The eye constantly needs to make tiny movements which are below the detection level of conscious perception in order for us to see well. While microsaccades were once considered a laboratory artifact, modern experiments have shown their value in human visual fixation. [Matinez-Conde]. Microsaccades are the largest and fastest of the so-called fixational eye movements, which also include drift and tremor [ref]. Microsaccades' magnitude may reach and sometimes be larger than 1 deg of visual angle, occurring at a rate of 1–2 Hz. There seems to be a clear continuum from microsaccades to the largest exploratory saccades in terms of neural generating substrate [ref] and, even saccadic intrusions, rapid involuntary devofeating and refoveating saccades that interrupt fixation, observed in certain neurodegenerative disorders but also in healthy subjects, share similarities with microsaccades [ref].

How to record microsaccades? Paradoxical interest in microsaccades over the past decades has mainly been on how to correct for them in order to optimize high resolution retinal imaging. The practical solution was the invention of incorporating eye tracking functionality to retinal imaging tools. Microsaccades are registered and ill placed images are dropped. So one easy and cost effective way to get a quantitative handle of microsaccades would be to get a read out from the eye tracker data of the OCT machine [Axel, ?provide ref]. The Green lab from UCSF developed a novel approach to monocular recording and quantification of microsaccades, a custom-built retinal eye-tracker. However, the reader should be aware that commercially available instruments of binocular recording such as video-oculography (e.g., EyeLink 1000, SR research) compare at the same level of search-coil techniques when it comes to microsaccades' detection [McCamy et al ].

The last two decades have seen an impressive body of literature on microsaccades, as defining the properties of visual fixation, a less navigated field of oculomotor and visual science, could lead to a deeper understanding of pathologies of the afferent and efferent visual systems that result in abnormal fixation. The paper from the UCSF group is the latest in a series of works aimed at characterizing changes of microsaccades dynamics in ophthalmic and neurological disease, from attention-deficit hyperactivity disorder (ADHD) and amblyopia to neurodegenerative disorders, such as progressive supranuclear palsy [Otero Millan], Alzheimer disease and MS [Mallery]. The paper by Sheehy et al. is relevant in the field of MS as markers of early disease, as well as indicators of disease progression complementing the MRI, are needed to help provide an individualized prognosis in affected patients. The authors found that patients with MS show an increased rate of microsaccades compared to healthy controls. They suggest this could be due to damages within the gaze holding mechanism regulated by the brainstem and cerebellum. This

conclusion has to be taken cautiously. Indeed, while recording in animals and modeling show that microsaccades are triggered by the superior culliculus [ref], the cerebellum (particularly the fastigial oculomotor region) might be heavily involved in improving microsaccades' accuracy [Sun]. On the other hand, microsaccades' rate was found to be increased in subjects with ADHD [Fried, Panagiotidi]. Thus, further studies should clarify if cognitive and attention impairment, common in MS, might be a contribuotr to changes in rate of microsacccades.

Extensive correlative statistical analyses presented by Sheehy et al. suggest that quantitative data on microsaccades relates to different degrees of disability in patients with multiple sclerosis. This adds to the field of eye movements, where it is known that ocular motor abnormalities correlate to a higher level fo disability [Leigh]. The authors conclude that microsaccades "provide objective measurements of MS disability level and disease worsening". In absence of a yet clear anatomical or network correlate for microsaccades, future studies need to tease out in more detail those most relevant pathological features. Obvious candidates are the internuclear ophthalmoplegia, but also cognition may play a role.

The technically versed and critical reader may make use of the partnership this Journal has started with Publons (https://publons.com/about/home/), which permits to read the referees' comments. These criticisms aside the work from the UCSF opens yet, after microcystic oedema (MMO) in 2012 [Axel, ?ref], another exciting field for future research in multiple sclerosis.