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Letter to the Editor

GABAAergic dysfunction in the olivary-cerebellar-brainstem network may cause eye oscillations and body tremor

Opsoclonus and flutter are ocular oscillations consisting of continuous, involuntary, conjugate saccades without intersaccadic intervals. If these saccadic oscillations are purely horizontal, they are called ocular flutter; if they have horizontal, vertical and torsional components, they are called opsoclonus. Behavioral disturbances, cerebellar ataxia, and limb tremor may co-occur. Several infectious, paraneoplastic, metabolic, and toxic etiologies cause these disturbances, but how neural circuits generate the oscillations is not clear. Two main hypotheses for the pathomechanism of opsoclonus/flutter have been proposed on the basis of different clinical and experimental observations. In the first, reduction of glycinergic inhibition generates oscillations in the positive feedback loop between saccadic brainstem burst neurons (Shaikh et al., 2007). In the second, disinhibition of cerebellar fastigial nuclei induces unwanted saccades through excitatory projections to the burst neurons (Wong et al., 2001). However, both theories remain controversial because they were not confirmed by lesion studies in animals, clinical findings, or model simulations (Lemos and Eggenberger, 2013). Analysis of high-resolution eye movement recordings from patients with opsoclonus/flutter might clarify the underlying mechanisms, but these are extremely rare.

Here, novel observations from two patients with opsoclonus and body tremor subsequent to performance-enhancing substance abuse suggest that eye and body oscillations may be generated by a GABAergic dysfunction of the olivary-cerebellar-brainstem network. The study was approved by the local ethics committee and informed consent was obtained from the patients.

Two tennis-players developed opsoclonus/flutter after a few months of self-administration of performance-enhancing substances. Patient 1, a 32-year-old male, presented with rapid onset of behavioral disturbances, vertigo, ataxia, head tremor, and opsoclonus causing visual blur and oscillopsia (Supplementary Video 1). Patient 2, a 34-year-old male, showed rapid progression of limb and axial tremor, vertigo, mood changes, ataxia, and ocular flutter (Supplementary Video 2). Common infectious, toxic, paraneoplastic, and metabolic causes of opsoclonus/flutter were excluded by negative brain MRI, blood, and CSF exams. Both patients reported an analogous typology, supply, and use of the enhancing chemicals, but only patient 1 provided a sample of the compound for testing, which led to the identification of anabolic androgenic steroids (AAS): nandrolone, stanozolol, and testosterone propionate. Treatment with intravenous IgG and benzodiazepine led to recovery in three-to-four weeks in both patients.

In patient 2, limb tremor characterized by tonic motor activity at 8 Hz was recorded by electromyography (EMG) from the extensor carpi radialis, during maintenance of the antigravity position of the arm (Fig. 1A). High resolution eye movement recordings from the same patient (pt 2) showed fixation interrupted by frequent horizontal saccadic pulses (back-to-back saccades without intersaccadic interval, Fig. 1B, label P), as well as horizontal macro-square-wave jerks (back-to-back saccades separated by intersaccadic intervals). The saccadic intrusions sometimes passed the midline, causing macrosaccadic oscillations around the target (Fig. 1 B, label S). In some cases, saccadic pulses transitioned from sharply peaked pulses to flattened pulses, evolving into macrosaccadic oscillations (Fig. 1C).

The patient also had an exceptional saccadic intrusion consisting of hybrid, spindle-shaped oscillations at 3.6 ± 0.3 Hz with amplitudes ranging from 9° to 37° (Fig. 1D). Saccades in this spindle were separated by an intersaccadic interval on the right side but not on the left side, so that the oscillations appeared as a hybrid of macrosaccadic oscillations on the right side and saccadic pulses on the left side (a *square-pulse* waveform). A similar co-occurrence of hybrid oscillations with and without intersaccadic intervals was seen in an earlier paper, but was not remarked upon (Helmchen et al., 2003).

Reflexive saccades toward horizontal target displacements were hypermetric and followed by saccadic oscillations (Fig. 1E). Small, uncorrelated ocular tremor was present on both horizontal and vertical axes ($p < 0.001$; horizontal: 45.1 ± 19.1 Hz, amplitude = 0.24 ± 0.15° vs. vertical: 39.3 ± 17.7 Hz, amplitude = 0.26 ± 0.14°) (Fig. 1F). The velocity/amplitude main sequence for saccades was normal, whereas the oscillations of the ocular tremor did not follow a saccadic velocity/amplitude main sequence (Fig. 1G).

Hypermetric saccades and macrosaccadic oscillations imply an impairment of the ipsilateral fastigial nucleus (Quaia et al., 1999). On the other hand, saccadic pulses indicate hyperexcitability of premotor burst cells and lack of omnipause neurons activation (Shaikh et al., 2007).

In our cases, the AAS association suggests that these impairments might be due to a GABAergic dysfunction. Indeed, AAS affect neuronal activity by both acute and chronic actions on the $GABA_A$ receptors, with effects varying specifically on their α, δ and ε subunit composition and GABA concentration (Oberlander et al., 2012). AAS induce allosteric modulation of the channels and alter $GABA_A$ receptor subunit expression and function (Oberlander et al., 2012). Moreover, AAS affect the immune system by altering antibody and cellular functions (Brenu et al., 2011). Thus, AAS might increase the risk of autoimmune pathological mechanisms in the central nervous system, targeting $GABA_A$ receptors. $GABA_A$ receptors, with α subunit composition vulnerable to AAS, are present on the forebrain, omnipause, olivary, and cerebellar neurons (Pirker et al., 2000). Different subunit composition and GABA availability at synaptic and extra-synaptic GABA receptors might

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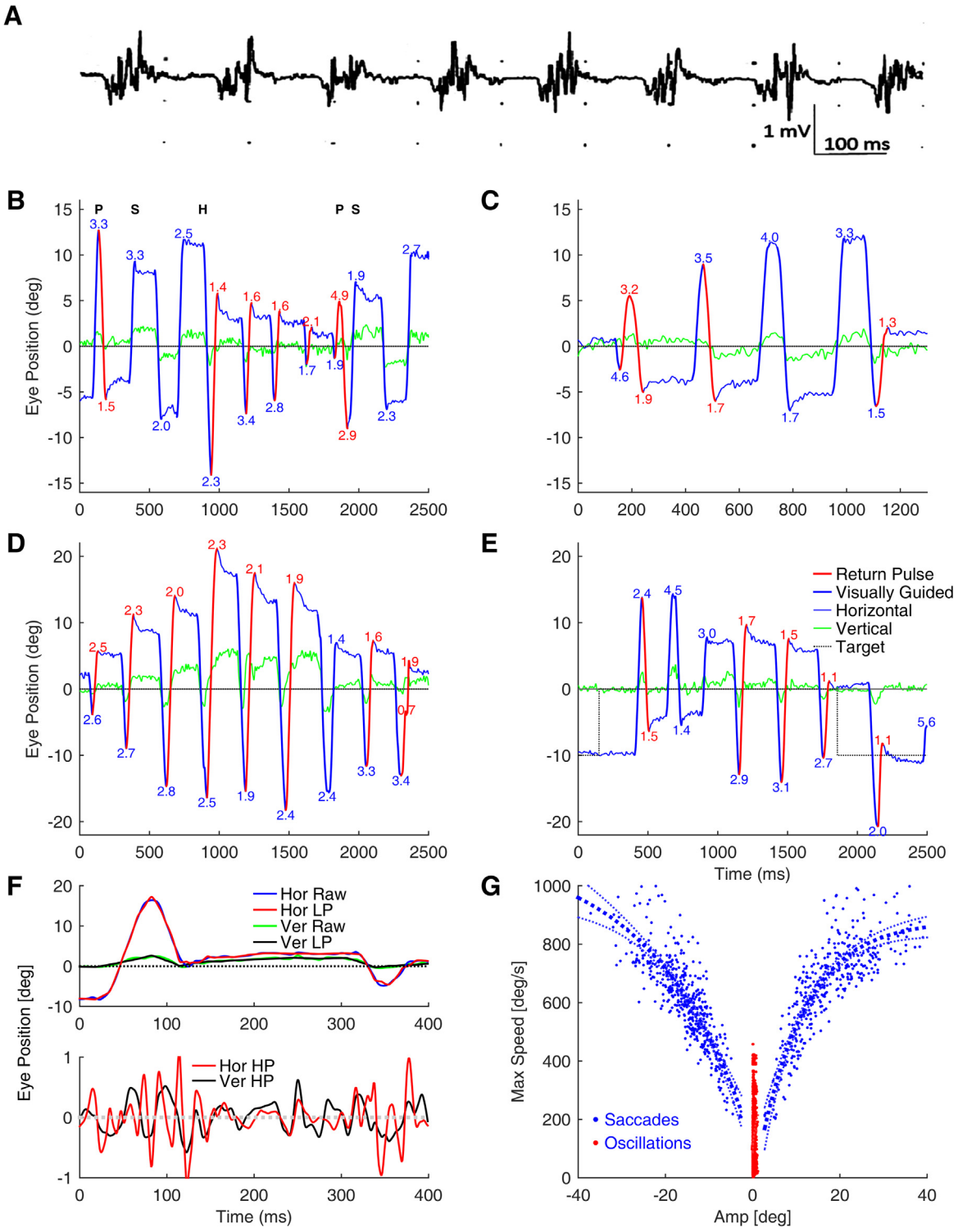

Fig. 1. Limb and eye oscillations of patient 2. (A) Surface EMG from the extensor carpi radialis, during maintenance of the antigravity position of the arm, shows periodic motor activity at 8 Hz. (B) Eye position was recorded at 240 Hz by an ASL 504 eye-tracker device (Applied Science Laboratories, Bedford, MA, USA) during fixation and saccadic tasks. Video-oculography shows saccadic pulses (back-to-back saccades without a pause, P), macrosaccadic oscillations (saccades separated by a normal intersaccadic interval, S), and a hybrid oscillation (saccades with and without pauses alternating, H). Numbers by each saccade indicate the gain of that movement, assuming the saccade is aimed at the fixation point. The directions of saccadic pulses and macrosaccadic oscillations could reverse, indicating a bilateral dysfunction with unbalanced, alternating severity. (C) Saccadic pulses transitioning from sharp to flat pulses, evolving into a macrosaccadic oscillation, possibly suggesting a gradual re-acquisition of function of the omnipause neurons. (D) Spindle-shaped oscillations. Rightward saccades are followed by an intersaccadic interval (as in macrosaccadic oscillations), whereas no intersaccadic interval follows leftward saccades (as in ocular flutter). (E) Visually-guided saccades (blue) were severely hypermetric. (F) Small amplitude, high frequency ocular tremor was present on the horizontal and vertical axes. Upper panels show raw data in blue, and low-pass filtered data in red. The lower panels show the residuals after subtracting the filtered from the raw data. Horizontal tremor was faster than vertical tremor. (G) Visually guided saccades and saccadic pulses (blue dots) showed a typical main sequence, whereas oscillations of the ocular tremor (red dots) did not. Dashed and dotted curves are the best-fit exponential and its 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

explain a diverse alteration of these brain areas because of a direct or immune-mediated effect of the AAS.

Accordingly, antibodies against $GABA_A$ receptors ($\alpha1/\beta3$ subunits) have been recently found in opsoclonus, supporting a GABAergic dysfunction as possible cause (Petit-Pedrol et al., 2014).

In conclusion, opsoclonus/flutter might be caused by GABAAergic dysfunction leading to fastigial hypofunction and reduced omnipause neuron excitability. Reduced fastigial GABAAergic inhibition might also increase the electrotonic coupling within groups of olivary neurons, possibly causing ocular and body tremor (Lefler et al., 2014). Moreover, GABAAergic dysfunction of the forebrain could lead to the behavioral changes typically associated with opsoclonus. AAS might increase the risk of developing opsoclonus/flutter by altering the $GABA_A$ channels of these structures and/or favoring autoimmunity against $GABA_A$ receptors. This possibility is clinically relevant because of the broad use of these drugs.

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Conflict of interest: The authors declare no competing financial interests.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2016.12.014.

References

Brenu EW, McNaughton L, Marshall-Gradisnik SM. Is there a potential immune dysfunction with anabolic androgenic steroid use?: A review. Mini Rev Med Chem 2011;11:438–45.

Helmchen C, Rambold H, Sprenger A, Erdmann C, Binkofski FfMRI study. Cerebellar activation in opsoclonus: an fMRI study. Neurology 2003;61:412–5.

Lefler Y, Yarom Y, Uusisaari MY. Cerebellar inhibitory input to the inferior olive decreases electrical coupling and blocks subthreshold oscillations. Neuron 2014;81:1389–400.

Lemos J, Eggenberger E. Saccadic intrusions: review and update. Curr Opin Neurol 2013;26:59–66.

Oberlander JG, Penatti CA, Porter DM, Henderson LP. The buzz about anabolic androgenic steroids: electrophysiological effects in excitable tissues. Neuroendocrinology 2012;96:141–51.

Petit-Pedrol M, Armangue T, Peng X, Bataller L, Cellucci T, Davis R, et al. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol 2014;13:276–86.

Pirker S, Schwarzer C, Wieselthaler A, Sieghart W, Sperk G. GABA(A) receptors: immunocytochemical distribution of 13 subunits in the adult rat brain. Neuroscience 2000;101:815–50.

Quaia C, Lefevre P, Optican LM. Model of the control of saccades by superior colliculus and cerebellum. J Neurophysiol 1999;82:999–1018.

Shaikh AG, Miura K, Optican LM, Ramat S, Leigh RJ, Zee DS. A new familial disease of saccadic oscillations and limb tremor provides clues to mechanisms of common tremor disorders. Brain 2007;130:3020–31.

Wong AM, Musallam S, Tomlinson RD, Shannon P, Sharpe JA. Opsoclonus in three dimensions: oculographic, neuropathologic and modelling correlates. J Neurol Sci 2001;189:71–81.

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