# The metabolic topography of essential blepharospasm

## A focal dystonia with general implications

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**Article abstract—***Objective:* To determine the metabolic topography of essential blepharospasm (EB). *Background:* EB is a cranial dystonia of unknown etiology and anatomic localization. The authors have used $^{18}$F-fluorodeoxyglucose (FDG) and PET with network analysis to identify distinctive patterns of regional metabolic abnormality associated with idiopathic torsion dystonia (ITD), as well as sleep induction during PET imaging to suppress involuntary movements, thereby reducing this potential confound in the analysis. *Methods:* Six patients with EB and six normal volunteers were scanned with FDG-PET. Scans were performed twice: once in wakefulness and once following sleep induction. The authors used statistical parametric mapping to compare glucose metabolism between patients with EB and control subjects in each condition. They also quantified the expression of the previously identified ITD-related metabolic networks in each subject in both conditions. *Results:* With active involuntary movements during wakefulness, the EB group exhibited hypermetabolism of the cerebellum and pons. With movement suppression during sleep, the EB group exhibited superior-medial frontal hypometabolism in a region associated with cortical control of eyelid movement. Network analysis demonstrated a specific metabolic covariance pattern associated with ITD was also expressed in the patients with EB in both the sleep and wake conditions. *Conclusion:* These findings suggest that the clinical manifestations of EB are associated with abnormal metabolic activity in the pons and cerebellum, whereas the functional substrate of the disorder may be associated with abnormalities in cortical eyelid control regions. Furthermore, ITD-related networks are expressed in patients with EB, suggesting a functional commonality between both forms of primary dystonia.

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Essential blepharospasm (EB) is a form of primary dystonia characterized by involuntary spasm of the musculature of the upper face.[1] The neuropathology of the condition is unknown, but the occurrence of blepharospasm has been reported in association with lesions in the thalamus,[2] lower pons,[3] and midbrain.[2,4] EB is considered to be a focal subtype of idiopathic torsion dystonia (ITD), which is associated

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with a number of genetic variants. We have used $^{18}$F-fluorodeoxyglucose (FDG) and PET with network analysis to study the metabolic topography of ITD,[5] with specific attention to the *DYT1*-linked variant of this disorder.[6] In these studies, we identified two metabolic networks associated with DYT1 dystonia: one expressed in mutation carriers irrespective of penetrance, and another expressed only in patients with clinical signs of dystonia. Because abnormal involuntary movements can be suppressed by sleep induction,[7] we used this method as a means of evaluating metabolic changes in ITD without this confound.[6] Indeed, the expression of the first DYT1 network was not altered by sleep induction, supporting its association with the underlying substrate of dystonia, and not with involuntary movement. By contrast, the second DYT1 network was suppressed by sleep induction, thus validating its association with the clinical manifestations of dystonia.

In the current study, we used sleep induction to investigate the metabolic substrate of EB. Comparisons between patient and control scans acquired in wakefulness were performed to identify metabolic changes associated with the presence of blepharospasm. Comparisons of patient and control scans acquired following sleep induction were performed to identify the underlying metabolic pathology of EB without the confound of concurrent abnormal involuntary movements. We also quantified the expression of the previously identified ITD-related networks in patients with EB and control subjects in both sleep and wakefulness. This comparison allowed us to determine whether network commonalities existed between EB and other forms of primary dystonia.

**Methods.** *Patient selection.* Six patients with EB (mean age 63.0 ± 10.6 years) were recruited through the Movement Disorder Center at North Shore University Hospital, Manhasset, NY. All patients had experienced symptoms for at least 2 years. The patients were not medicated at the time of the scans. Although all patients had previously been treated with botulinum toxin, the most recent treatment had been over 4 months before the imaging experiments. Six neurologically normal volunteers (mean age 54.2 ± 11.4 years) served as control subjects. Written informed consent was obtained from all participants under a protocol approved by the institutional review boards of North Shore University Hospital and New York University Medical Center.

*PET imaging.* All patients with EB and control subjects were scanned in both sleep and wakefulness, as previously described by our group.[6] PET studies in the two conditions were performed on consecutive days with the order of the two scans randomized between sessions.

Waking studies. Quantitative FDG-PET scan imaging in the waking state was performed in three-dimensional mode using a GE Advance tomograph[8,9] (GE Medical Systems, Milwaukee, WI) (resolution 4.2 mm full width half maximum in all directions, 35 slices, 15-cm axial field of view). To reduce head movement and repositioning errors, subjects were positioned in the scanner using a Laitinen stereoadapter (Sandstrom Trade and Technology, Welland, Ontario, Canada) with three-dimensional laser alignment. All studies were performed in a dimly lit room and with minimal auditory stimulation. The time course of $^{18}$F radioactivity was determined by sampling radial arterial blood. We calculated global and regional cerebral metabolic rates for glucose (GMR and rCMRGlc) in all FDG/PET studies on a pixel-by-pixel basis. Functionalized brain images were transformed into the Talairach coordinate system.[10]

Sleep studies. Quantitative FDG-PET imaging in sleep was performed as in wakefulness with identical stereoadapter settings in both sessions. Approximately 1 hour before the sleep experiment, each subject received between 100 mg and 200 mg of secobarbital orally. The sleep state was monitored with EEG recordings, and radiotracer was injected only after the subjects were judged to be in stage II sleep. Reduced muscle activity during the sleep scans was confirmed by concurrent surface electromyography. PET imaging proceeded as in the waking state. Sleep and wake studies were aligned automatically.[11]

*Data analysis.* Statistical parametric mapping. We used statistical parametric mapping (SPM96, Wellcome Department of Cognitive Neurology, London, UK) to form the following between-group comparisons: patients with EB and control subjects were compared in wakefulness to identify areas of abnormality in EB associated with the presence of active blepharospasm, and patients with EB and control subjects were compared in sleep to identify areas of abnormality associated with the metabolic substrate of the disorder without the confound of movement.

Between-group comparisons were considered significant at $p < 0.01$ if hypothesis driven and for $p < 0.001$ if not hypothesis driven. Hypothesis-driven searches were confined to regions associated with motor control pathways including the cerebellum, brainstem, thalamus, basal ganglia, and cortical motor regions including those associated with supernuclear control of eyelid movement.

Network analysis. In a previous study of DYT1 dystonia we identified two discrete metabolic networks associated with this condition.[6] The first was identified in an analysis of nonmanifesting DYT1 carriers and control subjects. This pattern was designated movement-free (MF) and was also abnormally expressed in patients with symptomatic dystonia. During sleep induction, the expression of this network remained elevated relative to sleeping control subjects. We also identified a second network that was expressed only in affected patients with DYT1 dystonia. This pattern was designated movement-related (MR); its expression was suppressed during sleep induction.

In this study, we used the Topographic Profile Rating (TPR) algorithm[12] to compute the expression (subject score) of the previously identified dystonia covariance patterns in the patients with EB and control subjects on an individual case basis. Thirty standardized regions of interest (ROI)[13] were placed on each set of brain slices by using an automated routine incorporating a count-thresholding algorithm, blind to scan condition.[6] (The TPR analysis used to compute the MF and MR subject scores in the EB and control cohorts was identical to that performed by us previously in the reported sleep studies conducted in patients with DYT1 dystonia.[6] This prospective analysis used ROI rather than voxel-based metabolic data, because the region weights on the MF and MR patterns used in TPR necessarily corresponded to the 30 ROI employed in the

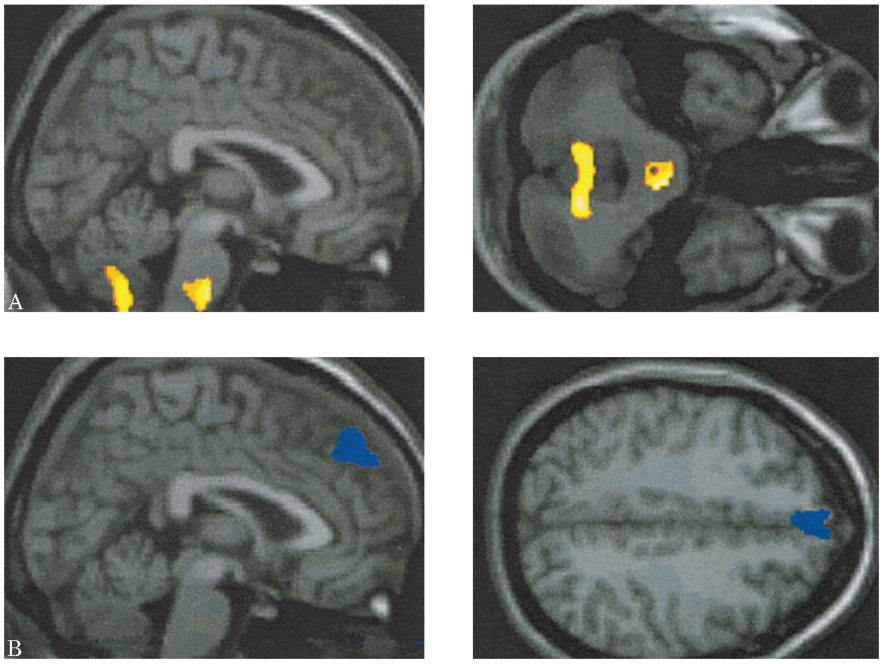


*Figure 1. Essential blepharospasm (EB). (A) Brain regions associated with significant metabolic increases in EB in wakefulness. Comparison of the EB and control groups scanned in wakefulness revealed localized increases (yellow scale) in the cerebellum and the pons of the patient group. (B) Brain regions associated with significant metabolic reductions in EB in sleep. Comparison of the EB and control groups scanned in sleep revealed localized decreases (blue scale) in Brodmann area 8 of the patient group. A threshold of* $p < 0.01$ *was set for statistical parametric mapping displays; see text.*

original identification of these topographies.) Identical ROI coordinates were used in the analysis of the functionalized images obtained in sleep and wakefulness. In each subject MF and MR subject scores were computed separately for the wakefulness and sleep conditions. Between-group comparisons of MF and MR subject scores were carried out using Student's *t*-tests and were considered significant at $p < 0.05$.

**Results.** *SPM analysis.* SPM comparisons of metabolism in EB and control groups scanned in wakefulness revealed the presence of significant increases in the cerebellum ($Z_{max} = 3.86$; x = 12, y = −62, z = −50 mm; $p < 0.0001$) and pons ($Z_{max} = 3.39$; x = 8, y = −28, z = −42 mm; $p < 0.0001$) of patients with EB relative to control subjects (figure 1A). No significant metabolic reductions were evident in the wakefulness comparison. SPM comparison of metabolism in the EB and control groups scanned in sleep revealed the presence of a significant reduction in the EB group localized to the superior-medial aspects of Brodmann area 8 of the premotor frontal cortex ($Z_{max} = 5.02$; x = −2, y = 52, z = 40 mm; $p < 0.0001$) (figure 1B). Significant metabolic increases in sleep were not evident in the EB group relative to normal subjects.

*Network analysis.* MF subject scores computed prospectively in our cohort were elevated in patients with EB relative to control subjects in both wakefulness and sleep ($p < 0.005$ for both comparisons; figure 2A). Prospectively computed MR subject scores did not differ significantly between the groups in either condition (figure 2B).

**Discussion.** Our findings suggest that functional similarities and differences exist between EB and more generalized variants of primary dystonia. Comparison of patients with EB and control subjects scanned in wakefulness demonstrates the presence of cerebellar and pontine metabolic increases in the disease group. This suggests that as a clinical phenomenon, blepharospasm is associated with abnormalities in brainstem and cerebellar functioning. This observation is consistent with the metabolic network abnormalities described by us in waking affected patients with DYT1 dystonia,[6] and accords with the results of electrophysiologic studies demonstrating enhanced excitability of the blink reflex in EB and other forms of dystonia.[14,15]

Because of the suppression of blepharospasm in sleep, the metabolic comparison of patients with EB and control subjects in this state may be more reflective of the underlying pathology of the condition. Interestingly, we found that the EB group was characterized by abnormal reductions in the superior-medial aspect of Brodmann area 8, a region associated with supranuclear control of eyelid opening.[16] We have not identified similar reductions in other forms of dystonia, suggesting that this abnormality may be specific for EB. We interpret this metabolic finding as suggesting disordered modulation of cortical control of eyelid movements. In a previous FDG-PET study of patients with isolated lid opening apraxia, we noted similar metabolic decrements in the medial frontal cortex.[17] In a number of these cases, the frontocortical abnormality was associated with concomitant striatal hypometabolism. Conceivably, the metabolic substrate of EB may relate to a loss of afferent projections to cortical lid control areas secondary to disordered basal ganglia output. Alternatively in EB, cortical inhibition in this region may be impaired as a primary abnormality. Functional imaging studies of larger cohorts of patients with EB incorporating models of functional connectivity may be useful in delineating these possibilities.[18] Likewise, MR spectroscopic measurements may determine whether a localized neurochemical

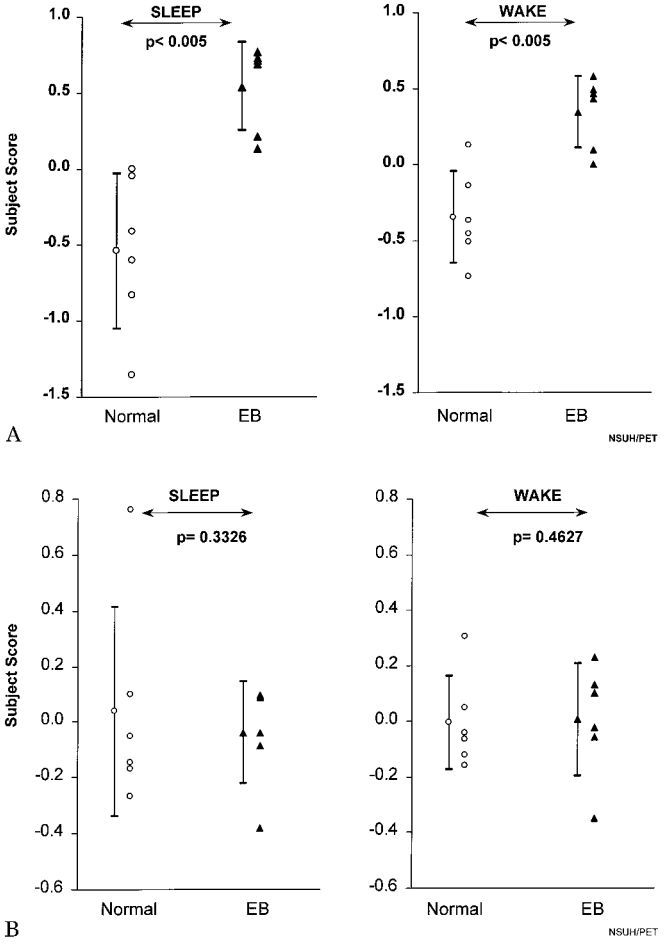


*Figure 2. (A) Scatter diagram of the subject scores for the DYT1 dystonia movement-free (MF) pattern computed prospectively in control subjects (open circles) and in patients with essential blepharospasm patients (filled triangles). MF pattern expression was significantly elevated (*$p < 0.005$*) in the EB group in comparisons conducted both in sleep (left panel) and in wakefulness (right panel). (See text.) (B) Scatter diagram of the subject scores for the DYT1 dystonia movement-related (MR) pattern computed prospectively in control subjects (open circles) and in patients with EB (filled triangles). No significant group differences were evident in comparisons conducted in either sleep (left panel) or in wakefulness (right panel). Error bars indicate SD.*

abnormality exists in patients with EB compatible with reduced activity of frontocortical inhibitory interneurons.

In previous studies we found that ITD, particularly the DYT1-linked variant, is associated with the expression of a specific MF covariance topography characterized by covarying overactivity of the lentiform nuclei, cerebellum, and the supplementary motor regions.[5,6] Because this pattern was found to be present in DYT1 mutation carriers irrespective of clinical penetrance, we originally hypothesized that it might represent a genotype-specific metabolic trait associated with dystonia. In the current study, we found that the MF pattern is also expressed in patients with EB, whether scanned during wakefulness or following movement suppression in sleep. This suggests that this pattern is not specific to any one genotype associated with ITD. Indeed, we recently found the MF pattern to be expressed in North American Mennonites with ITD associated with the DYT6 mutation.[19]

The MR pattern of DYT1 dystonia is characterized by covarying increases in the metabolic activity of the midbrain, cerebellum, and the thalamus.[6] In contrast to the MF pattern, this covariance pattern is not abnormally expressed in patients with EB, whether scanned in wakefulness or in sleep. We attribute this finding to the very different motor manifestations of these two forms of dystonia. We note, however, that in wakefulness the EB group manifested significant mean increases in the cerebellum and pons relative to control subjects. This suggests that although these regions may be active in EB, their functional interrelationship differs from that observed in more generalized forms of dystonia. In this vein, we note that hypermetabolism of the thalamus was not evident in our study of EB, even though this region contributed significantly to the MR network of DYT1 dystonia. This disparity might be attributable to the nature of the abnormal movements in the two conditions. Thalamic increases in wakefulness may be prominent in more severe forms of dystonia in which limb and trunk movements are associated with a greater degree of sensory feedback.

We acknowledge that these findings were obtained through the analysis of a limited number of patients with EB and control subjects and should be regarded as exploratory. This investigation focused on the identification of the primary metabolic abnormality in EB through FDG-PET scanning conducted both in sleep and in wakefulness. In a recent report, Esmaeli-Gutstein et al.[20] found metabolic increases in the basal ganglia and thalamus in awake patients with EB. It is not clear why analogous findings were not present in our patients when scanned in wakefulness. Conceivably, significant basal ganglia and thalamic abnormalities may be evident in more severely affected patients with EB. Nonetheless, this possibility cannot be assessed without comparison of PET findings in the cohorts of varying disease severity in whom standardized blepharospasm ratings were obtained. We also recognize that our network analysis in EB was restricted to the prospective quantification of the MF and MR patterns identified by us previously in DYT1 dystonia. With the scanning of larger numbers of patients with EB and control subjects in both sleep and wakefulness, enhanced statistical power may allow for the identification of new metabolic topographies that are specific for this form of dystonia.

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