

# GABAergic Dysfunction in Essential Tremor: An $^{11}\text{C}$ -Flumazenil PET Study

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Essential tremor is the most common movement disorder, but the underlying pathophysiology is not well understood. A primary overactivity of cerebellothalamic output pathways is the most conspicuous finding, as indicated by animal and human studies. It has been argued that this overactivity may be due to impaired central inhibition, and converging evidence points toward a potential role of  $\gamma$ -aminobutyric acid (GABA) dysfunction in tremor generation. **Methods:** Using  $^{11}\text{C}$ -flumazenil and PET, we calculated the distribution volume, an index of availability of benzodiazepine receptor sites of the GABA<sub>A</sub> complex, in a group of 8 patients with bilateral essential tremor, as compared with 11 healthy controls. **Results:** Significant increases in binding of  $^{11}\text{C}$ -flumazenil at the benzodiazepine receptor site of the GABA<sub>A</sub> receptor in the cerebellum, the ventrolateral thalamus, and the lateral premotor cortex were identified in the essential tremor group. **Conclusion:** Essential tremor is associated with reduced GABAergic function and increased availability of benzodiazepine receptor sites in brain regions implicated specifically in tremor genesis. This finding is thought to reflect overactivity of cerebellothalamic circuits and, hence, lends support to the “GABA hypothesis” of essential tremor.

**Key Words:** tremor; GABA; flumazenil; PET

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**E**ssential tremor is the most common movement disorder (1), with prevalence estimates ranging from 4% in the population aged less than 40 y (2) to 14% in the population aged 65 y or more (3). Essential tremor is inherited in an autosomal-dominant pattern with high penetrance, and the clinical picture is dominated by a low-frequency 4- to 9-Hz postural or action tremor involving the hands, the head, and

other body parts (4,5). Recent data have challenged the traditional view of essential tremor's being a monosymptomatic disorder: although postural and kinetic tremors are still considered as the core symptomatology of essential tremor, other symptoms (e.g., cognitive deficits, psychiatric abnormalities, and ataxia) are increasingly recognized, and they increase the clinical diversity of essential tremor (6). Although the clinical course of essential tremor is usually slowly progressive over decades, advanced disease stages can be physically and socially highly disabling and warrant effective treatment.

There is human postmortem evidence that essential tremor is associated with pathology at the level of the cerebellum and interconnected circuits: although patients show no macroscopically discernible cerebellar atrophy (7), microscopic cerebellar pathology has been identified, including gliosis, Purkinje cell loss, and increased torpedoes (swellings) in the Purkinje cell axons (6,8–10). Activation studies with PET indicate abnormally increased regional cerebral blood flow in the cerebellum both at rest and when tremor is provoked by unilateral arm extension (11,12,42,43). This bilateral cerebellar overactivity distinguishes essential-tremor patients from healthy volunteers, in whom mimicking of unilateral tremor or passive unilateral wrist oscillation by an experimenter causes predominantly ipsilateral cerebellar activation (11,12). Cerebellar involvement in essential tremor is also supported by work with MRI, including spectroscopy (13), voxel-based morphometry (14), and functional MRI (15).

Despite this progress in characterizing the overactive neuronal networks in essential tremor, the underlying pathogenesis is not yet known. Different lines of evidence point toward a disturbance of the inhibitory neurotransmitter  $\gamma$ -aminobutyric acid (GABA) in essential tremor (16). This “GABA hypothesis” is based on the GABAergic action of some drugs with tremorolytic properties, altered GABA concentrations in human cerebrospinal fluid from essential-tremor patients (17), and recent genetic findings in knockout

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mice suggesting that the gene coding for the GABA<sub>A</sub>  $\alpha_1$ -receptor subunit is a potential candidate gene for essential tremor (18).

The aim of the present study was to investigate whether the GABA hypothesis is supported by in vivo imaging. Dynamic PET images of a group of essential tremor patients and healthy controls were acquired using the radioligand <sup>11</sup>C-flumazenil, which binds specifically to the central benzodiazepine receptor site of the GABA<sub>A</sub> receptor complex. From this, parametric distribution volume images were calculated to test our hypothesis of focally altered <sup>11</sup>C-flumazenil binding at sites of tremor genesis, in particular at the level of the cerebellum and interconnected thalamocortical pathways.

## MATERIALS AND METHODS

### Subjects

The study protocol was approved by the ethics committee of the medical faculty of the Technische Universität München and the national radiation protection authorities. Written informed consent according to the Declaration of Helsinki was obtained from each participant after full explanation of the procedures involved.

We investigated 8 patients (4 male, 4 female; mean age, 65.5 ± 8.0 y) fulfilling the criteria for definite essential tremor according

to the proposal of the Tremor Research and Investigation Group (19), namely longstanding (>5 y) bilateral visible and persistent postural tremor with or without kinetic tremor involving hands or forearms. Neurologic examinations ruled out enhanced physiologic tremor and extrapyramidal signs indicative of Parkinson disease. None of the patients had a history of psychiatric disease, and exclusion criteria included sudden tremor onset, exposure to tremorgenic drugs, tremor induced by trauma, or features suggestive of psychogenic tremor. Outside the PET scanner, patients were evaluated with the Clinical Rating Scale for Tremor, part 1 (20), and tremor frequency was measured with surface electromyography recording electrodes attached at the wrist flexor and extensor muscles of the most affected outstretched arm (Keypoint EMG; Medtronic).

The patients were scanned while not receiving medication. Any medication that might interact with the GABA<sub>A</sub> receptor was withdrawn before PET, accounting for the respective half-lives of the compounds listed in Table 1. Thus, we can exclude pharmacologic interference with the GABA<sub>A</sub> receptor at the time of PET. The PET scans were acquired at rest without tremor. All demographic and clinical details of the patients are summarized in Table 1. A control group of 11 healthy volunteers (5 male, 6 female) with no history of neurologic or psychiatric diseases was studied for comparison, after exclusion of 1 volunteer because of technical problems. Their mean age at examination was 56.6 ± 4.3 y. None of the volunteers had a history of alcohol or substance abuse, and

**TABLE 1.** Demographic and Clinical Characteristics of Essential Tremor Patients

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Sex	M	M	F	F	M	M	F	F
Age (y)	71	71	66	53	62	55	73	73
Handedness	R	R	R	R	R	R	L	R
Essential tremor family history	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Disease duration (y)	52	10	6	7	30	40	50	43
Tremor distribution	UE (LE)	UE	UE	UE	UE	UE	UE	UE
Tremor characteristics	Postural	Postural/kinetic	Postural/kinetic	Postural/kinetic	Postural/kinetic	Postural/kinetic	Postural	Postural/kinetic
Dominant side of tremor (UE)	R > L	L > R	L > R	R > L	L > R	R > L	L = R	L > R
Tremor frequency (UE) (Hz)	6	6	6	8	5	5	6	6
Tremor amplitude (UE)*	3	4	3	2	2	3	4	2
Head tremor	Mild	None	Mild	None	Mild	Mild	Moderate	Mild
Vocal tremor	None	None	Moderate	None	Mild	None	Severe	None
Current tremor medication	GP	None	None	None	None	None	None	MP
Previous tremor medication†	None	PR; P	None	None	P	PR; GP; P	MP; P	None
Alcohol responsiveness	Yes	Not known	Not known	No	Yes	Yes	Yes	Yes
TSH, basal (mU/l)	0.6	1.5	3.4	0.2‡	1.3	0.5	0.5	1.8
CRST, part 1	31	42	27	12	22	25	43	26

\*Tremor amplitude, derived from CRST, point 3: arms outstretched, wrist mildly extended, fingers spread apart (0 = none; 1 = slight amplitude [ $<0.5$  cm], may be intermittent; 2 = moderate amplitude [ $0.5$ – $1$  cm], may be intermittent; 3 = marked amplitude [ $1$ – $2$  cm]; 4 = severe amplitude [ $>2$  cm]).

†Withdrawn before PET, accounting for respective half-lives of compounds.

‡Measured in patient receiving 25  $\mu$ g of levothyroxine-natrium for goiter therapy.

CRST = Clinical Rating Scale for Tremor (20), with maximum of 80 points for part 1; UE = upper extremities; LE = lower extremities; PR = propranolol; P = primidone; GP = gabapentin; MP = metoprolol; TSH = thyroid-stimulating hormone.

there was no intake of substances interfering with the GABA<sub>A</sub> receptor before PET.

### PET Image Acquisition

<sup>11</sup>C-flumazenil was radiosynthesized by a modification of a method described previously (21), and the <sup>11</sup>C-flumazenil PET images were acquired using a procedure described in detail elsewhere (22). The PET data were acquired in 3-dimensional mode with an ECAT EXACT HR+ (CTI PET Systems) scanner over 90 min with the following frame durations: 12 × 5 s, 5 × 60 s, 3 × 180 s, 5 × 300 s, and 5 × 600 s, for a total of 30 frames. The data were reconstructed using filtered backprojection into 63 slices of 2.4-mm thickness (pixel size, 2.1 × 2.1 mm) with an image matrix size of 128 × 128 pixels. The resolution of the reconstructed images was approximately 6 mm in full width at half maximum. Emission data were corrected for random coincidences, scatter, attenuation, and radioactive decay. Head position was permanently monitored using a video system and reference marks and, if necessary, manually adjusted.

### PET Data Analysis

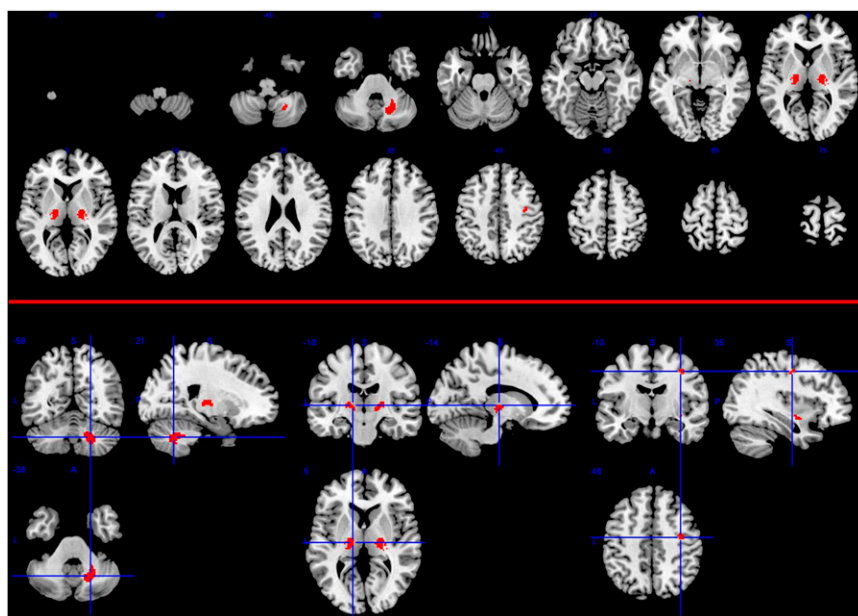
The time series of each subject's dataset were realigned to a reference frame (frame 20) with a high signal-to-noise ratio by means of a least-squares approach and a 6-parameter spatial transformation as implemented in SPM 8 (Wellcome Trust Centre for Neuroimaging), using default settings to minimize movement artifacts. Parametric images of <sup>11</sup>C-flumazenil distribution volume (mL·cm<sup>-3</sup>) reflecting binding to GABA<sub>A</sub> sites at a voxel level were calculated from these time series and the metabolite-corrected arterial plasma input function using Logan graphical analysis (23). This analytic approach enables a quantitative description of GABA<sub>A</sub> receptor availability in the human brain at a voxel level (22) and allows for voxel-based group comparisons in normal and pathologic conditions. The distribution volume images were spatially normalized using a ligand-specific template (24) in Montreal Neurologic Institute standard space. The normalization algorithm involved a least-squares approach and a 12-parameter spatial transformation followed by estimating nonlinear

deformations. A fourth-degree B-spline function was used for interpolation. Finally, the images were smoothed with a 12 × 12 × 12 mm (full width at half maximum) isotropic gaussian kernel.

SPM 8 was used to localize statistical differences between <sup>11</sup>C-flumazenil binding at a voxel level between the essential tremor patients and the healthy controls. A 2-sample *t* test was applied, without grand mean scaling or global normalization. A threshold was applied to the images at a relative value of 0.8. To exclude any potential effect of age on <sup>11</sup>C-flumazenil binding, this variable was treated as a covariate of no interest. A conservative statistical threshold of *P* < 0.05 (familywise error-corrected) was used for whole-brain analysis (cluster extent threshold, *k* > 10). Additionally, we performed a region-of-interest-based analysis of <sup>11</sup>C-flumazenil binding status that was confined to a set of regions previously implicated in tremor generation (tremor network: cerebellum, medulla, pons, midbrain, thalamus, basal ganglia, and premotor/primary sensorimotor cortices). In this region-of-interest analysis, we applied a conservative statistical threshold of *P* < 0.05, familywise error-corrected (cluster extent threshold, *k* > 10). The regions of interest were derived from the Wake Forest University PickAtlas software, version 2.4 (<http://fmri.wfubmc.edu/cms/software#PickAtlas>).

## RESULTS

In the essential tremor patients, the whole-brain analysis identified significantly increased <sup>11</sup>C-flumazenil binding in the left ventrolateral thalamus at the level of the ventral intermediate nucleus. Additionally, the extended region-of-interest analysis revealed a significantly increased <sup>11</sup>C-flumazenil binding in the right ventrolateral thalamus, the right dentate nucleus, and the right premotor cortex (Fig. 1; Table 2). Figure 2 details the individual <sup>11</sup>C-flumazenil binding values at these maxima (Montreal Neurologic Institute coordinates, Table 2) for patients and healthy controls. Neither the basal ganglia nor the sensorimotor cortex (Fig. 1) showed significant changes in <sup>11</sup>C-flumazenil binding.



**FIGURE 1.** SPM analysis of changes in <sup>11</sup>C-flumazenil binding in essential-tremor group. Regions of abnormally increased <sup>11</sup>C-flumazenil binding in patients, compared with healthy controls, are seen in ventrolateral thalamus, dentate nucleus, and premotor cortex (*P* < 0.05: extended region-of-interest analysis; familywise error-corrected; extent threshold, *k* > 10). Changes in <sup>11</sup>C-flumazenil binding are most prominent in subcortical regions.

**TABLE 2.** GABA<sub>A</sub> Receptor Binding Changes in Essential Tremor Patients

Cluster no.	Extent (voxel)	Anatomic region	Hemisphere	<i>P</i>	<i>z</i> score	Montreal Neurologic Institute coordinate (x, y, z; mm)
1*	104	Thalamus, ventrolateral	L	0.016	4.07	−18, −16, 2
2	249	Cerebellum, dentate nucleus	R	0.019	4.01	22, −56, −40
		Cerebellum, dentate nucleus	R	0.031	3.86	18, −50, −34
3	117	Thalamus, ventrolateral	R	0.026	3.92	20, −16, 2
		Thalamus, ventrolateral	R	0.033	3.84	24, −24, 6
4	27	Middle frontal gyrus, Brodmann area 6	R	0.027	3.90	36, −10, 44

Relative increases in <sup>11</sup>C-flumazenil binding in essential tremor patients, compared with healthy controls. Delineated are all regions that reached significance level of *P* < 0.05 after familywise error correction and cluster extent threshold of *k* > 10 in region-of-interest-based analysis of cerebellum, medulla, pons, midbrain, thalamus, basal ganglia, and premotor/primary sensorimotor cortices. Regions significant at *P* < 0.05, familywise error-corrected, on whole-brain analysis are marked by asterisk. Montreal Neurologic Institute coordinates, in millimeters, describe location of peak voxel in each cluster.

Importantly, our analysis revealed neither significant (*P* < 0.05, familywise error-corrected) nor trend (*P* < 0.001, uncorrected) effects in the opposite contrast (essential tremor patients < healthy controls). Thus, there was no indication of locally decreased <sup>11</sup>C-flumazenil binding in essential tremor.

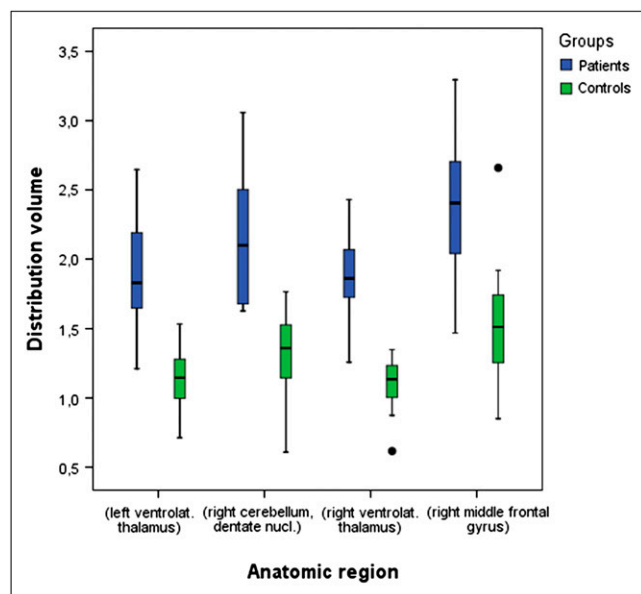
## DISCUSSION

A neurotransmitter disturbance affecting the balance between excitatory and inhibitory neuronal activity in tremor-related networks has been suspected in essential

tremor. GABA is the principal inhibitory transmitter in the central nervous system, and drugs facilitating GABA transmission inhibit harmaline-induced tremor in animals (25). Likewise, in essential tremor patients, the tremolytic responses to ethanol (26) and gabapentin (27) support the role of the GABAergic system. Here, we provide evidence of focally increased <sup>11</sup>C-flumazenil binding at the benzodiazepine receptor site of the GABA<sub>A</sub> receptor, thereby lending in vivo support to an underlying GABAergic dysfunction. We have confirmed, in this larger independent cohort, preliminary case-based accounts of upregulated <sup>11</sup>C-flumazenil binding in the ventrolateral thalamus (11) while monitoring GABA<sub>A</sub> receptor status in subtentorial regions.

The <sup>11</sup>C-flumazenil binding changes were located in regions implicated in tremor genesis, for example, the thalamus at the level of the ventral intermediate nucleus, the cerebellum at the level of the dentate nucleus, and the lateral premotor cortex. Although motor and premotor (28,29) cortical areas are part of the synchronized brain network in essential tremor, the <sup>11</sup>C-flumazenil binding changes were expressed preponderantly in subcortical areas. Animal studies with the agent harmaline and lesions targeting the dentatorubroolivary tract cause 4- to 8-Hz tremor and, thus, support the pivotal role of the cerebellum in tremor generation (30). Clinical case studies showed that lesions involving the cerebellum (31) or the thalamus (32) can effectively alleviate tremor in essential tremor patients. The ventral intermediate nucleus is the most effective target for stereotactic interventions in tremor control, and rhythmic overactivity correlated with tremor profiles has been identified in the ventral intermediate thalamus in essential-tremor patients undergoing thalamotomy (33). The regions where we encountered thalamic <sup>11</sup>C-flumazenil binding changes correspond well with this location (Fig. 1).

Microinjections of the GABA<sub>A</sub> agonist muscimol into the ventral intermediate thalamus of essential tremor patients undergoing stereotaxy are effective in reducing tremor (34), supporting the view of a local deficiency of GABA<sub>A</sub>-



**FIGURE 2.** Box plots of individual data for essential tremor patients and healthy controls. Data are <sup>11</sup>C-flumazenil binding values at Montreal Neurologic Institute coordinates, as presented in Table 2. Green boxes indicate distribution volumes of healthy controls, and blue boxes indicate those of essential tremor patients. nucl. = nucleus; ventrolat. = ventrolateral.



mediated thalamic neuronal inhibition. Tremorlysis can also be temporarily induced by repetitive transcranial magnetic stimulation of the cerebellum (35), which is presumed to induce locally increased GABA levels (35). The dendritic spines of the inferior olivary cells receive GABAergic input from the deep cerebellar nuclei, and modulating the activity of these systems may "... increase or decrease the population of neurons that entrained at a particular frequency, thus increasing or decreasing the amplitude of the tremor oscillation" (35). Thus, the tremorlytic effects induced by increasing GABAergic transmission in the thalamus and the cerebellum suggest that our  $^{11}\text{C}$ -flumazenil PET findings in these specific areas are not an epiphenomenon but are related to the core pathology of essential tremor.

It is, however, unlikely that essential tremor arises from a primary deficiency of GABAergic neurotransmission. Rather, the observed pattern of localized increased  $^{11}\text{C}$ -flumazenil binding in essential tremor may reflect a reactive receptor upregulation related to a localized GABAergic deficit, for instance related to the cerebellar Purkinje cell loss identified in postmortem studies (6,8–10). Alternatively, the increased  $^{11}\text{C}$ -flumazenil binding might reflect a functional abnormality at the level of GABA<sub>A</sub> receptor subtypes. These are formed by at least 16 different subunits, and there is a marked variation in their distribution throughout the brain, with the  $\alpha_1$ -receptor subtype being most abundant (36). Because these multiple GABA<sub>A</sub> receptor subtypes all respond to GABAergic input, the genetic inactivation of one of the various GABA receptor subunits will not be lethal but will most likely affect only specific cells in selective parts of the brain (37). Recent animal models of essential tremor support a causal link to an abnormal GABA<sub>A</sub> receptor configuration. The gene encoding the  $\alpha_1$ -subunit of the GABA<sub>A</sub> receptor was knocked out in a transgenic mice model with a targeted deletion of the  $\alpha_1$ -subunit ( $\alpha_1^-/\alpha_1^-$ ). These mice do not express the  $\alpha_1$ -receptor subunit protein and exhibit a 15- to 19-Hz action tremor (18). These ( $\alpha_1^-/\alpha_1^-$ ) mice are characterized by stable adaptations in the expression of other GABA<sub>A</sub> receptor subunits, including decreased expression of  $\beta_{2/3}$ - and  $\gamma_2$ -subunits and increased expression of  $\alpha_2$ - and  $\alpha_3$ -subunits (18). Thus, in this model there is altered expression of alternative GABA<sub>A</sub> receptor  $\alpha$ -subunits, compensating the knocked-out  $\alpha_1$ -subunit.

It cannot be answered with surety whether the increased  $^{11}\text{C}$ -flumazenil binding pattern observed here reflects a general receptor upregulation as a consequence of a local GABAergic deficit or whether it reflects a specific upregulation of selected GABA<sub>A</sub> receptor subtypes as a local compensatory mechanism to an abnormal GABA<sub>A</sub> receptor configuration. As with any PET ligand, it is impossible to distinguish whether increased ligand binding results from decreased competition with GABA transmitter or an increased number or increased affinity of GABA<sub>A</sub> receptors. Although our findings may well be in line with an upregulation of selected GABA<sub>A</sub> receptor subtypes, it is impossible

to specify abnormal GABA<sub>A</sub> receptor configurations by means of  $^{11}\text{C}$ -flumazenil PET. In contrast to the endogenous neurotransmitter GABA, flumazenil binds reversely with high affinity to the benzodiazepine site of GABA<sub>A</sub> receptors containing the  $\alpha_1$ -,  $\alpha_2$ -,  $\alpha_3$ -, or  $\alpha_5$ -subunits, and less so to those containing  $\alpha_4$ - or  $\alpha_6$ -subunits (38). Despite this uncertainty, it is intriguing that  $\alpha_1^-/\alpha_1^-$  transgenic mice and patients with essential tremor respond to similar drugs (e.g., propranolol, primidone, and gabapentin), whereas the most significant tremorlytic effect in transgenic mice can be induced by low, nonsedating dosages of alcohol (18). This is an important analogy to the tremorlytic effect of alcohol in alcohol-responsive essential tremor patients—an effect that is presumed to be mediated by GABAergic mechanisms as well. Ethanol reduces essential tremor amplitude in up to 67% of patients, whereas the efficacy of diazepam is far lower (39). This finding implies that alcohol is not acting solely via central benzodiazepine receptor agonistic action but may also have other effects—for example, suppressing sodium ion channel activity (40) or transiently decreasing nerve membrane conductance (41). Using  $\text{H}_2^{15}\text{O}$  PET, we showed that ethanol reduces the abnormally elevated cerebellar regional cerebral blood flow in essential tremor patients, thereby reducing the inhibitory input in the deep cerebellar nuclei. Reduced inhibitory input in the deep cerebellar nuclei might cause increased cerebellar inhibitory output to the inferior olivary nuclei as a potential mechanism of tumor suppression (12).

## CONCLUSION

We provide neuroimaging evidence of abnormally increased GABA<sub>A</sub> receptor binding in essential tremor that is potentially linked to the rhythmic overactivity within the cerebellothalamic output pathways. Our data support the GABA hypothesis of essential tremor using *in vivo*  $^{11}\text{C}$ -flumazenil PET in humans, extending the indirect measures derived from animal studies of tremor or the local microelectrode recording data. The increased  $^{11}\text{C}$ -flumazenil binding in cerebellothalamic pathways anatomically overlaps previous  $\text{H}_2^{15}\text{O}$  PET regional cerebral blood flow increases (12,42,43) and raised metabolism (44,45). Yet, our data demonstrate a local GABAergic dysfunction in humans, thus providing an independent measure of pathophysiologic and treatment-related interest in essential tremor. Extending these studies to at-risk subjects for essential tremor or using deep brain stimulation to test whether the changes in flumazenil binding are normalized after this procedure would provide a means to understand whether the binding changes are primary or secondary phenomena.

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