The Functional Neuroanatomy of Anxiety: A Study of Three Disorders Using Positron Emission Tomography and Symptom Provocation

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Previous neuroimaging research has contributed insights regarding the neural substrates of specific psychiatric disorders. The purpose of this study was to determine the shared mediating neuroanatomy of anxiety symptoms across three different anxiety disorders. Data were pooled from 23 right-handed adult outpatients meeting criteria for obsessive-compulsive disorder, simple phobia, or posttraumatic stress disorder. Relative regional cerebral blood flow (rCBF) was measured using positron emission tomography in the context of symptom provocation paradigms. Symptom severity was measured via self-reports. The analysis of pooled imaging data indicated activation in right inferior frontal cortex, right posterior medial orbitofrontal cortex, bilateral insular cortex, bilateral lenticulate nuclei, and bilateral brain stem foci during the symptomatic versus control conditions. A positive correlation was found between rCBF at one brain stem locus and subjective anxiety scores ($r = .744$, $p < .001$). These findings suggest that elements of the paralimbic belt together with right inferior frontal cortex and subcortical nuclei mediate symptoms across different anxiety disorders. In addition, activation at one brain stem locus appears to be associated with the subjective severity of anxiety. Further studies are warranted to determine whether these same brain systems mediate normal anxiety states as well.

Key Words: Anxiety, limbic system, obsessive-compulsive disorder, phobia, positron emission tomography, posttraumatic stress disorder

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Introduction

We have previously presented results from positron emission tomography (PET) symptom provocation studies of obsessive-compulsive disorder (OCD) (Rauch et al 1994), simple phobia (SP) (Rauch et al 1995), and posttraumatic stress disorder (PTSD) (Rauch et al 1996). A summary of the findings from these three previous studies is presented in Tables 1 and 2. The purpose of the current study was to determine the mediating neuroanatomy of anxiety symptoms across these three different anxiety disorders by analyzing pooled data from the combined cohort.

Although pathological anxiety states may be mediated by systems unique to each disorder, we hypothesized that

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Table 1. Demographic and Behavioral Data from Three PET Symptom Provocation Studies of Anxiety Disorders

Primary diagnosis/study	OCD	SP	PTSD	Total
Number of subjects	8	7	8	23
Gender (male:female)	5:3	1:6	2:6	8:15
Right-handed	All	All	All	All
Age (mean ± SEM) (years)	36.1 ± 2.0	37.0 ± 3.9	41.1 ± 3.4	38.1 ± 1.8
Teeth-clenching control	$n = 0$	$n = 1$	$n = 8$	$n = 9$
AAS score (mean ± SEM)				
Provoked	5.1 ± 0.9	5.1 ± 1.5	9.6 ± 0.2	6.7 ± 0.6
Control	1.9 ± 0.5	1.0 ± 0.9	0.2 ± 0.1	1.0 ± 0.3
Difference	3.3 ± 1.0	4.1 ± 0.5	9.4 ± 0.3	5.7 ± 0.7

a core system might mediate anxiety nonspecifically across a variety of disorders. Moreover, this same system may mediate physiological (i.e., normal) anxiety states as well. We proposed that such a core anxiety system might comprise elements of the paralimbic belt (i.e., posterior medial orbitofrontal, anterior cingulate, insular, parahippocampal, and anterior temporal cortex; see Mesulam 1985) together with other structures thought to modulate emotion and/or arousal (Papez 1937; Mesulam 1985; Gorman et al 1989; Davis 1992; Charney et al 1993). Because this represents an analysis of pooled data from previous studies, no truly a priori hypotheses can be claimed. The benefit of this approach, however, is that it enables us to exploit the considerable statistical power afforded by a large data set compiled over several years, all within the context of a common experimental design. As a consequence of this enhanced statistical power, additional loci of activation may become apparent that were undetectable with smaller cohorts. Furthermore, to assess the relationship between blood flow changes and subjective ratings of anxiety, a meaningful correlation analysis becomes feasible.

Table 2. Summary of Activation Profiles from Three PET Symptom Provocation Studies of Anxiety Disorders

Region	OCD study	Simple phobia study	PTSD study
Medial orbitofrontal			
Anterior	Left	—	—
Posterior	Right	Left	Right
Anterior cingulate	Left	Right	Right
Insula	—	Left	Right
Temporal			
Anterior	—	Right	Right
Medial	—	—	Right
Amygdala	—	—	Right
Caudate	Right	—	—
Thalamus	—	Left	—
Visual cortex	—	—	Right
Sensorimotor cortex	—	Left	—

"Right" or "left" designates the laterality of statistically significant activation (in the OCD study, $p < .05$, adjusted for multiple comparisons; others are $p < .001$, uncorrected) for the corresponding brain region. "—" indicates that no significant activation was found within the corresponding brain region.

Methods

As previously described (Rauch et al 1994, 1995, 1996), 23 right-handed adult outpatients (15 women, 8 men; mean age 38 years, range 22–55 years) meeting clinical criteria for OCD ($n = 8$), SP ($n = 7$), or PTSD ($n = 8$) were studied both during symptomatic (i.e., provoked) and control conditions. Written informed consent was obtained from each subject prior to participation and all procedures were carried out in accordance with the Subcommittee on Human Studies of Massachusetts General Hospital. Provocative stimuli included elements of in vivo exposure and/or mental imagery. The stimuli were individually tailored to each subject's clinical presentation and were developed with their cooperation. Control conditions were matched with respect to sensorimotor and cognitive features. For instance, in the case of OCD, patients with contamination obsessions were touched with a "contaminated" object during the provoked condition, versus a "clean" version of the same object during the control condition; in the case of SP, subjects with small animal phobias were exposed to a container housing the feared animal during the provoked condition, versus the empty container during the control condition; and, in the case of PTSD, patients listened to audiotaped narratives describing their traumatic event immediately preceding the provoked scan, versus narratives describing neutral daily activities for the control scans (see Rauch et al 1994, 1995, 1996).

For 1 subject in the SP study, and all 8 subjects in the PTSD study, additional teeth-clenching control data were obtained to help identify extracranial artifacts (Drevets et al 1992). Self-report anxiety analog scale (AAS) scores were obtained for each scan.

PET data were acquired via a Scanditronix PC4096 whole body tomograph (General Electric, Milwaukee, WI)

Table 3. Brain Regions Exhibiting Significantly Increased Activation Associated with Provocation of Anxiety Symptoms Based on Pooled Data from Three Studies

Brain region	*Z* score/maximum pixel value[a] (provoked minus control)	Maximum pixel, coordinates[b]
Medial orbitofrontal (right/posterior)	4.19	22, 17, −16
Inferior frontal (right)	3.82	45, 20, −4
Insular cortex		
Right	3.89	29, 17, −16
Left	4.23	−39, 5, 0
Lenticulate		
Right	3.54	25, −9, 8
Left	3.98	−31, −5, −4
Brain stem		
Right	4.16	4, −39, −16
Left	3.98	−12, −17, −4
Midline/bilateral	4.26	−3, −22, 0

[a]Values represent the actual maximum pixel value (in *Z*-score units) within the brain region from the statistical parametric map. Regional activations with *Z* scores > 3.00 correspond to $p < .001$, uncorrected for multiple comparisons; *Z* scores > 3.50 correspond to approximately $p < .05$, with Bonferroni-type correction for multiple comparisons. All activations with *Z* scores ≥ 3.00 are listed.

[b]Coordinates defining the location of the maximum pixel values within each brain region from the provoked minus control statistical parametric-map in Talairach space are expressed as "x, y, z"; x > 0 is right of the midsagittal plane, y > 0 is anterior to the anterior commissure, and z > 0 is superior to the anterior commissure–posterior commissure plane.

in its stationary mode. Patients were imaged twice in each condition, with their eyes closed, during inhalation of oxygen- 15-labeled carbon dioxide for 1 min.

Whole-brain-normalized images reflecting relative regional cerebral blood flow (rCBF) were transformed to Talairach space (Talairach and Tournoux 1988; Alpert et al 1993), and a statistical parametric map (SPM) was generated for the symptomatic minus control contrast, with units in *Z* score (Rauch et al 1994, 1995, 1996; Friston et al 1991). The SPM was systematically inspected to identify foci of activation achieving *Z*-score thresholds of >3.0, corresponding to $p < .001$, uncorrected for multiple comparisons (i.e., many pixels). More stringent criteria (e.g., *Z* scores > 3.5–4.0, depending on the number of resolution elements in the total search volume) correspond to a Bonferroni-corrected statistical threshold of approximately $p < .05$. Pearson product-moment correlation analyses were performed to test associations between rCBF and anxiety scores. The rCBF values for the correlation analyses were determined according to previously published procedures (Rauch et al 1994); targeted circular regions of interest (ROIs) of fixed diameter (five pixels) were placed around foci of significant activation, and the mean rCBF value from within the relevant ROI was computed.

Results

PET data were available from all 23 subjects: replicates for each condition were available for 5 OCD, 4 SP, and all 8 PTSD subjects; a single scan in each condition was available for the remaining 6 subjects (i.e., a total of 40 scans per condition, rather than 46). Note that replicates for each subject are averaged as an initial step in the statistical mapping procedure, so that each subject contributes equally to the group SPM. A complete set of corresponding AAS scores was available from all subjects.

Foci of significant activation in the provoked minus control state were found in right inferior frontal cortex, right posterior medial orbitofrontal cortex, bilateral insular cortex, bilateral lenticulate nuclei, and bilateral brain stem (see Table 3 and Figure 1).) Moreover, the actual observed *Z* scores exceeded 3.5 for all of these sites. No other foci of activation achieved the threshold of *Z* score > 3.0.

A statistically significant positive correlation was found between rCBF at the left brain stem locus and AAS score ($r = .744$, df = 21, $p < .001$; see Figure 2). This finding remained statistically significant when the probability was adjusted for multiple comparisons (i.e., $.001 \times 9 = .009$; nine correlations tested). No statistically significant relationship was found between rCBF and AAS score for any of the other eight foci of activation (all $p > .1$).

Structures in the vicinity of this left brain stem focus include the motor nucleus of cranial nerve V. Therefore, rCBF at this locus and relevant AAS scores were compared across control, teeth-clenching, and provoked conditions for the subjects from whom such data were available ($n = 9$). Significant rCBF differences existed between the provoked versus control as well as the provoked versus teeth-clenching conditions ($p < .05$), but not between teeth-clenching and control conditions

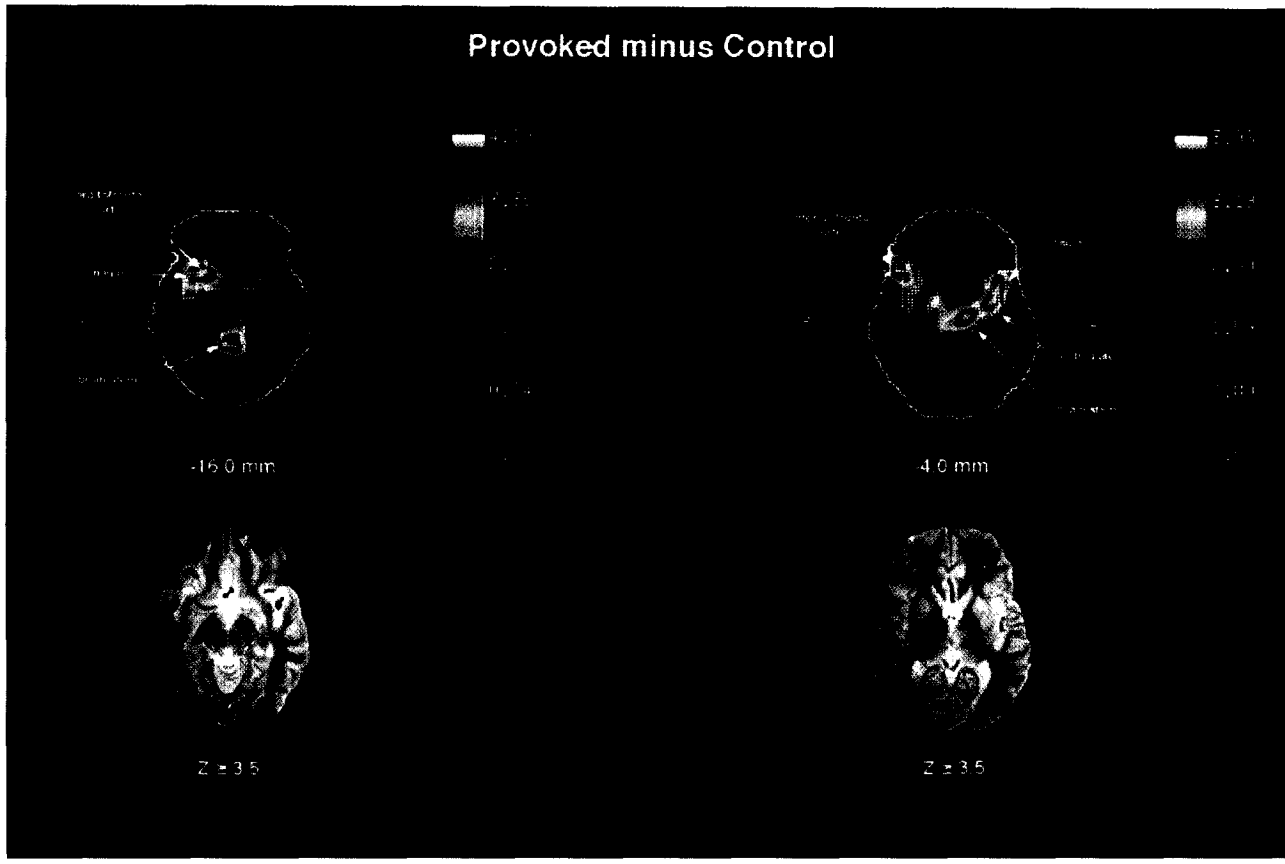

Figure 1. PET statistical parametric map of provoked minus control conditions for pooled data from three anxiety disorders. Horizontal slices from the statistical parametric map, at 16 and 4 mm inferior to the anterior commissure-posterior commissure plane respectively, are oriented according to neuroimaging convention (top = anterior; bottom = posterior; right = left; left = right), and each is displayed in two ways. In the upper panels, *Z*-score values are illustrated via a Sokoloff color scale. White dashed outlines reflecting the boundaries of brain regions of interest, as defined via a digitized version of the Talairach atlas, are superimposed for anatomical reference; solid lines demarcate the boundaries of the whole brain slice. In the lower panels, contiguous pixels exceeding a *Z*-score threshold of 3.5 (corresponding to approximately $p < .05$, corrected for multiple comparisons) are shown in red. The findings are superimposed over a structural (T2-weighted) magnetic resonance image transformed to Talairach space for approximate anatomic reference. The magnetic resonance reference image is from a nominally normal subject, who did not participate in these PET studies.

($p > .05$), paralleling the pattern of AAS values rather than the pattern of teeth-clenching.

Discussion

The results suggest that: 1) elements of the paralimbic belt, right inferior frontal cortex, and subcortical nuclei mediate symptoms across different anxiety disorders; 2) rCBF within the left brain stem focus is most closely associated with the magnitude of subjective anxiety; and, 3) further studies are needed to determine the specificity of these findings with respect to pathological versus physiological (i.e., normal) anxiety states.

The present study entailed a within-subject design (i.e., provoked versus control states in each subject) and did not include a normal control group. Therefore, it is not possible to conclude that the observed pattern of activation is unique to pathological anxiety states. To the contrary, one interpretation of the current findings is that the observed activation profile reflects a core physiological anxiety system that is also recruited in pathological conditions. In fact, Benkelfat and colleagues have recently presented findings from an anxiety-induction PET study of normal subjects (Benkelfat et al 1995). They found rCBF increases in anterior cingulate cortex as well as a broad territory referred to as the claustrum-insular-amygdala region associated with cholecystokinin$_4$-induced anxiety, and in orbitofrontal cortex associated with anticipatory anxiety. Thus, Benkelfat and colleagues' results converge with those of the current study; both found activation in orbitofrontal cortex, and territories spanning bilateral insular cortex and lenticulate/claustrum. Benkelfat and colleagues cautioned that their claustrum-insular-amygdala activation could not reliably be attributed to parenchymal

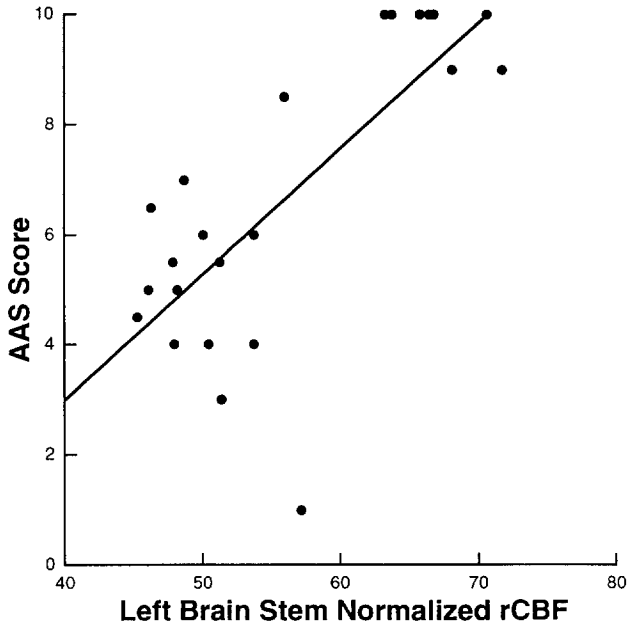

Figure 2. Anxiety analog scale score versus normalized regional cerebral blood flow. The scatter plot illustrates a positive correlation ($r = .744$, df = 21, $p < .001$) between AAS score and rCBF at the left brain stem locus; each point represents the mean values for 1 subject during their provoked condition.

changes in CBF versus cerebral blood volume changes from larger vessels (Benkelfat et al 1995). The same caveat must be acknowledged regarding the current findings, although there is no evidence that they are artifactual. In fact, a role for insular cortex in mediating anxiety is quite plausible (Rauch et al 1995; Mesulam 1985; Kaada 1960; Kaada et al 1949; Mesulam and Mufson 1982); however, lateral lenticulate (i.e., putamen) activation is less easily rationalized. Current conceptualizations of corticostriatal pathways emphasize paralimbic and limbic inflow via the ventral striatum (i.e., nucleus accumbens), whereas the putamen primarily participates in the sensorimotor circuit (Alexander et al 1986, 1990). Still, the patch-matrix scheme of striatal compartmental organization acknowledges a major projection from limbic, paralimbic, and prefrontal territories through all components of the neostriatum (including the putamen), specifically ramifying in striatal striosomes (Graybiel 1990; Gerfen 1992).

Benkelfat and colleagues also questioned whether their cingulate activation was specific to anxiety, or instead a substrate of attentional changes, given the absence of correlation with anxiety ratings (Benkelfat et al 1995). Interestingly, in the current investigation, we failed to find activation in anterior ciqgulate cortex, despite having detected significant rCBF increases in each of the individual studies (Rauch et al 1994, 1995, 1996) contributing to this pooled analysis. Given that the cingulate is a large structure, one important point is that the precise location of cingulate activation differed across our three previous studies, although all corresponded approximately to Brodmann areas 24 and/or 32. Various other cortical regions project to different subterritories of the anterior cingulate. Therefore, we propose that the topography of cingulate rCBF increases may reflect which specific additional cortical regions are involved in the overall pattern of activation. Consequently, although no single locus within cingulate cortex participated in the symptomatic state across the groups studied, anterior cingulate cortex may still play a critical role in anxiety, or nonspecifically as a substrate of attentional allocation in the face of anxiety. There are abundant data, regarding electrical stimulation and lesions, which support the hypothesis that the anterior cingulate does play some role in anxiety states (e.g., Kelley 1980; Laitinen 1979; Baer et al 1995; Cosgrove and Rauch 1995).

Although we have focused on anxiety, the provoked states in these studies were characterized by a complex constellation of negative emotions, not limited to anxiety (see Rauch et al 1996). There are recent data regarding the activation profiles associated with other negative emotional states in normal subjects. George et al (1995) employed similar techniques to study happiness and sadness in healthy women. In association with transient sadness, they found rCBF increases in cingulate cortex, orbitofrontal cortex, striatum, and thalamus, as well as rCBF decreases in right temporal and bilateral occipital cortex. Studying a mixed-gender cohort, Pardo et al (1993) reported activation of inferior frontal and lateral orbitofrontal cortex associated with self-induced dysphoria; women exhibited bilateral activation, whereas the activations were predominantly left-sided for men. These data would seem to suggest that other intense emotional states may also be mediated by inferior frontal and paralimbic cortex, as well as components of striatum. Moreover, lateralization of function may be gender-influenced. There is a preexisting literature that espouses right-hemispheric dominance in the mediation of emotion (e.g., Ross 1985; Silberman and Weingartner 1986; Tomarken et al 1992; Liotti and Tucker 1995). Consistent with that view, we have found a predominance of right-sided paralimbic and inferior frontal activation in studies of SP (Rauch et al 1995) and PTSD (Rauch et al 1996), as well as in the current overall analysis. In all three cases, the subjects were predominantly female. Nonetheless, these studies do not, nor were they designed to, formally address the potential influence of gender on laterality.

To our knowledge, the only other PET study of anxiety to detect brain stem activation also involved symptom induction and a statistical parametric mapping data analytic method (Reiman et al 1989). Reiman and colleagues

studied rCBF changes associated with lactate-induced panic attacks in patients with panic disorder and found activation in bilateral brain stem (in the vicinity of the superior colliculi), as well as bilateral insula/claustrum/putamen. Although Reiman et al (1989) accomplished this feat in an analysis of only 8 subjects, they employed somewhat more liberal significance thresholds (actual Z scores = 1.73–2.84). Thus, although such brain stem findings are not unprecedented, it may require relatively large numbers of subjects (or more modest statistical thresholds) to demonstrate brain stem activation associated with anxiety.

In the current study, the left brain stem locus represents the only activation for which rCBF values were statistically correlated with subjective anxiety ratings. The teeth-clenching data provided strong evidence against the possibility that this simply reflected activation of the trigeminal motor nucleus as a correlate of teeth-clenching. The observed activation is located in the vicinity of several other structures purported to modulate arousal or autonomic tone, including the locus coeruleus, the parabrachial nucleus, the ventral tegmental area, and central grey (Davis 1992). The resolution of the methods used precludes identification of the specific structure or structures involved on this spatial scale. Still, it is possible that future research involving pharmacologic manipulations together with neuroimaging might help to dissect the brain stem structures that mediate arousal generally and anxious states in particular.

Other limitations of these methods have been acknowledged previously (Rauch et al 1994, 1995, 1996): the technique of signal normalization to whole brain, although reducing variance and obviating the issue of whole brain pCO_2 correction, does not allow for detection of changes in whole brain CBF. In fact, it remains unclear whether changes in respiratory rate, pCO_2, and whole brain CBF might confound findings in studies such as this, which rely on normalized CBF values. Moreover, localization of change in rCBF is constrained by the spatial resolution of PET, and the technique of stereotaxic transformation further compromises precise anatomic localization. Nonetheless, the advantages of this technique remain: the capability to sum data across subjects and allowing for the superior power associated with identifying locations of differential activation via the SPM data analytic approach.

In this study, the very detection of brain stem activations, as well as the identification of a strong correlation between rCBF and AAS scores, was a consequence of the greater statistical power generated by averaging data from a relatively large number of subjects. In future neuroimaging research, it may be critical to study large numbers of subjects to delineate all major components of relevant neural systems. Similarly, it will be important to advance methods that allow for acquisition and meaningful statistical treatment of data sets from individuals, so that interindividual differences can be more fully appreciated.

In summary, the current findings reflect an analysis of pooled PET data from three previous symptom provocation studies of three different anxiety disorders. The results lend new insights not appreciable from simple review of the earlier studies. The overall provoked minus control contrast demonstrated activation in right inferior frontal cortex, right posterior medial orbitofrontal cortex, bilateral insula, and bilateral lenticulate, as well as multiple brain stem foci. Interpreted in the context of previous research, these results support the hypothesis that paralimbic structures play a critical role in mediating anxiety across pathological conditions; this may reflect the role of paralimbic structures in a core neural system that mediates anxiety physiologically. The current findings also support models of right-sided dominance in mediating emotional functions and underscore the need to consider gender composition in interpreting neuroimaging results. Finally, the detection of brain stem activations, and the strong correlation between subjective anxiety ratings and rCBF at one brain stem locus, provide an intriguing, but inconclusive glimpse regarding the role of human brain stem nuclei in mediating anxiety or arousal. Additional studies will be necessary to replicate and expand upon the current findings. In particular, advances in imaging methods will be needed to enhance our capacity for probing human brain stem physiology in vivo and documenting individual differences between subjects.

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