
Evidence for Disturbed Cortical Signal Processing and Altered Serotonergic Neurotransmission in Generalized Anxiety Disorder

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Background: Current pathophysiological concepts of generalized anxiety disorder (GAD) assume a disturbed exteroceptive sensory system. Furthermore, central serotonergic neurotransmission has been shown to play an important role in anxiety disorder. Cortical signal processing as measured by auditory evoked potentials (AEPs) may reflect the integrity of the exteroceptive sensory system. Because a special aspect of AEP, the loudness dependence of the N1/P2-component (LD), has been related to central serotonergic activity, the LD may be useful for investigating serotonergic dysfunctions in GAD.

Methods: The LD was recorded in 31 medication-free patients with GAD without any psychiatric co-morbidity and in 31 matched control subjects. Dipole source analysis was performed to separate the LD of regions including the primary (LD-tangential dipole) and regions including the secondary auditory cortex (LD-radial dipole).

Results: A shallower LD-tangential was observed in patients with GAD as compared to healthy control subjects [$F(1,60) = 6.727$, $p = .012$; one-way analysis of variance]. The LD-radial showed no differences between groups. Severity of the anxiety symptoms was not related to the LDs.

Conclusions: The results indicate an altered exteroceptive sensory system in GAD occurring at the level of the primary but not secondary auditory cortex. Because a shallow LD of the primary auditory cortex was related to a high firing rate of neurons in the dorsal raphe nucleus, the results may support evidence for an enhanced serotonergic activity in GAD. *Biol Psychiatry* 2003;53:304–314 © 2003 Society of Biological Psychiatry

Key Words: Generalized anxiety disorder, serotonin, auditory evoked potentials, loudness dependence, dipole source analysis, anxiety inventory

Introduction

With a lifetime prevalence of 4.1%–6.6%, generalized anxiety disorder (GAD) is a common psychiatric disease in the general population (Brawman-Mintzer and Lydiard 1996; Kessler et al 1994). Neurophysiological and neurobiological aspects of anxiety disorders have become an extensive focus of research in the last decade. In this context, a relationship between central serotonergic (5-HT) neurotransmission and anxiety has been seen as an important pathophysiological aspect (Charney and Deutch 1996; Deakin 1998; Lesch et al 1996).

The role of 5-HT on anxiety has been observed extensively in animal studies. For example, a decrease of anxious behavior in rats was observed after destruction of central serotonergic neurons by administration of 5,7-dihydroxytryptamine (Briley et al 1990). Moreover, a generalized 5-HT depletion with p-chlorophenylalanine led to a reduction of aversive behavior of mice in the black and white test box (Barnes et al 1992). Handley (1995) extensively reviewed studies dealing with the effects of 5-HT–manipulating substances on anxiety and concluded a predominantly positive relationship between 5-HT neurotransmission in higher cortical regions and anxiety-related processes. Studies in humans also report evidence for 5-HT involvement in GAD. The nonspecific 5-HT₁ and 5-HT₂ receptor agonist m-chlorophenylpiperazine led to increased anxiety and hostility in GAD (Germine et al 1992). Furthermore, a reduced platelet paroxetine binding was observed in GAD (Iny et al 1994). A growing body of evidence supports the therapeutic efficacy of selective serotonin reuptake inhibitors (SSRIs) in GAD (Pollack et al 2001), which gives further evidence for the involvement of 5-HT in anxiety; however, preclinical studies and the efficacy of SSRIs in GAD raise the question of whether anxiety disorder is related to a hyper- or a hypofunction of 5-HT neurotransmission (Connor and Davidson 1998; Stein and Stahl 2000).

Serotonin is proposed to be involved in the mediation of anxiety via pathways originating in the raphe nucleus

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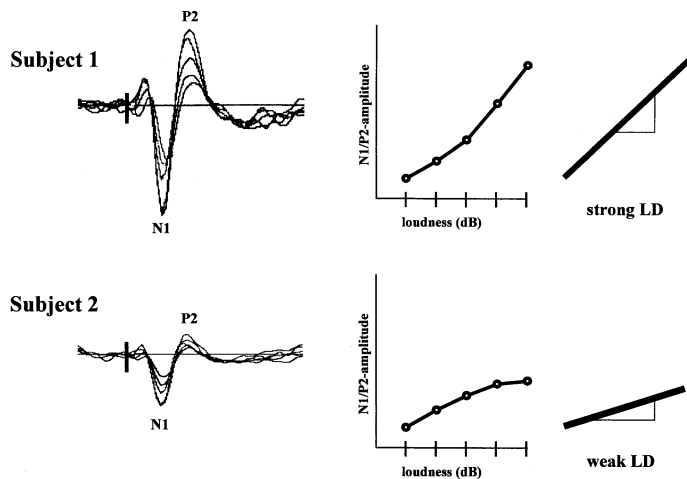


Figure 1. Illustration of two subjects with different loudness dependence (LD) of the auditory evoked N1/P2-component. The LD is the linear regression slope calculated from the five N1/P2-amplitudes. Subject 1 shows a steep LD (“augmenter”), whereas subject 2 possesses a shallow LD (“reducer”).

innervating the hypothalamus, thalamus, and the limbic system (Dubovsky and Thomas 1995). Other brain areas with a dense serotonergic innervation have not automatically been linked to the pathophysiology of anxiety. For example, primary sensory areas like the primary auditory cortex on Heschl’s gyrus are densely innervated by serotonergic fibers from the brainstem (Campbell et al 1987; Lewis et al 1986). It can be assumed that these regions change their physiology depending on serotonergic activity. In line with this, a relationship between brainstem serotonergic projections and initial auditory signal processing has previously been stressed (Morrison et al 1982). More specifically, the loudness dependence (LD) of the auditory evoked N1/P2-component, a special feature of auditory signal processing, has been related to central 5-HT activity. The LD denotes the amplitude change of evoked potentials (EPs) in response to different stimulus intensities (see Figure 1). The generator of the N1 is lying on Heschl’s gyrus, with the P2 generator about 5 mm more anterior, with an assumed origination in the primary auditory cortex (Näätänen and Picton 1987; Papanicolaou et al 1990; Tiitinen et al 1999). The relation between 5-HT and evoked potentials originating in the primary auditory cortex (see below) fits well with current concepts integrating the exteroceptive sensory systems into the functional neuroanatomy of anxiety and fear (Charney and Deutch 1996).

A great body of evidence from human and animal studies indicates a relationship between the LD and serotonergic activity (Bruneau et al 1986; Gallinat et al 2000; Hegerl and Juckel 1993; Juckel et al 1999; Manjarrez et al 2001; von Knorring and Perris 1981; Wang et al 1996). For example, a study of behaving cats found a decrease of the LD when applying the 5-HT_{1A}-receptor agonist 8-OH-DPAT and, conversely, an increase under the 5-HT₂-receptor antagonist ketanserin (Juckel et al 1997). It was also reported in behaving cats that the LD is

shallow during high firing rate of serotonergic neurons in dorsal raphe nucleus and vice versa (Juckel et al 1999). Although some evidence exists that other neuromodulators, such as dopamine and acetylcholine, affect the LD (Juckel et al 1997; Paige et al 1995), the most consistent relationship was reported with respect to 5-HT (for review see Hegerl and Juckel 1993). A steep LD is suggested to indicate a low serotonergic activity and vice versa. Of clinical interest are findings that patients with affective disorders show a favorable response to 5-HT agonistic agents such as lithium (Hegerl et al 1987, 1992) and SSRI (Gallinat et al 2000) when they possess a steep LD.

Methodologically important is the finding that experimental serotonergic manipulation affects the LD measured over the primary but not the secondary auditory cortex in animals (Juckel et al 1999). This is presumably owing to the denser serotonergic innervation of the primary as compared to the secondary auditory cortex (Campbell et al 1987; Lewis et al 1986). Therefore, a separation of the LD generated in the primary and secondary auditory cortex with dipole source analysis in human studies is advantageous when analyzing electroencephalogram (EEG) data. A well-established dipole model for the N1/P2-component with two dipole sources per hemisphere was previously described (Gallinat and Hegerl 1994; Scherg and von Cramon 1990). The dipole model of the N1/P2-component contains a tangential oriented dipole, representing the activity of regions including the primary auditory cortex, and a radial oriented dipole, representing the activity of regions including the secondary auditory cortex (Gallinat et al 2002). With respect to 5-HT, the LD of the tangential dipole (LD-tangential) is proposed to be the crucial parameter. A further advantage of dipole source analysis is the higher reliability of the LD-tangential ($r = .91$) (Gallinat and Hegerl 1994) as compared to the scalp-measured LD ($r = .60-0.78$) over a period of several

weeks (Friedman and Meares 1979a; Gallinat and Hegerl 1994).

We investigated 31 unmedicated outpatients with GAD according to DSM-IV criteria, and 31 healthy control subjects, matched with respect to age and gender. The N1/P2-component in response to five different intensities was recorded with 32 channels. Dipole source analysis of the N1/P2-component was performed to determine the LD of the primary (LD-tangential) and secondary auditory cortex (LD-radial) separately. The following hypotheses were tested: 1) the LD-tangential, as an indirect indicator of the serotonergic activity, in patients with GAD is significantly different from healthy control subjects; and 2) the LD-radial, which is not related to serotonergic activity, does not differ between patients and control subjects. Furthermore, we investigated whether the LD shows a relationship to psychopathology as measured by the Hamilton Anxiety Scale (Hamilton 1959), which was rated by an experienced investigator and the self-rating Spielberger State Trait Anxiety Inventory (STAI) (Laux et al 1981).

Methods and Materials

Subjects

This study was approved by the ethics committee of the Benjamin-Franklin-University Hospital of the Free University of Berlin. All subjects gave written informed consent after the procedure was fully explained to them.

Patients

Subjects for the present study were participating in a study on the efficacy of cognitive behavior therapy in the treatment of GAD. Inclusion criteria were that patients had to fulfill DSM-IV criteria for GAD (American Psychiatric Association 1994), had a minimum score of 18 on the Hamilton Anxiety Rating Scale (Hamilton 1959) at baseline examination, and were between 18 and 65 years of age. All subjects were outpatients and had no somatic disorders. Exclusion criteria were the presence of any other psychiatric illness, including other anxiety disorders, depressive disorder or personality disorders, the intake of psychotropic medication or another psychotherapy during the last 24 months, and hearing disorders. In all patients a urine test was drawn prior to the investigation to verify abstinence from benzodiazepines, barbiturates, and illegal drugs. Patients were recruited from collaborating general physicians or had directly contacted the anxiety call center of the research unit. Patients were examined by research assistants using standardized interviews and rating instruments. All ratings were assessed prior to the EEG recording. 31 patients (4 male, 27 female; mean age 47.7, SD 12.9, range 25–65 years) fulfilled these criteria. Their mean scores on the Hamilton Anxiety Scale were 24.0 (SD 6.4; range 18–51), Clinical Global Impression Scale (National Institute of Mental Health 1970) 3.8 (SD 0.7, range 3–6), Spielberger State Trait

Anxiety Inventory (STAI) (Laux et al 1981) state 50.4 (SD 10.4, range 27–77).

Healthy Control Subjects

A total of 245 healthy control subjects were recruited by newspaper advertisements and paid for their participation. To assess neuropsychiatric disorders, all healthy subjects were first questioned in a telephone interview by trained students using a structured questionnaire. In the next step, subjects were examined by an experienced psychiatrist in the Department of Psychiatry, Free University Berlin. The Mini-International Neuropsychiatric Interview (Sheehan et al 1998) was performed on all subjects. Subjects were excluded if they fulfilled the criteria of an Axis I diagnosis or were likely to have an Axis II diagnosis (Cluster A, B, or C). Further reasons for exclusion were severe internal or neurological diseases (e.g., Parkinson, non-compensated hypothyroidism, or diabetes mellitus), hearing disorders, or intake of psychotropic medication. Axis I diagnosis in first-degree relatives was also an exclusion criterion. For the present study, a sample of 31 subjects, matched with respect to age (mean age 48.7, SD 13.3, range 25–68 years) and gender, was drawn from the whole sample. Apart from other personality inventories, healthy subjects also performed the STAI, which was applied immediately prior to the beginning of the EEG recording. Two subjects had to be excluded from the further analysis of the STAI scores because of a lack of valid trials. The remaining 29 subjects had a STAI state mean score of 34.0 (SD 6.1, range 20–54).

AEP Recording

Recording took place in an electrically shielded and sound-attenuated room adjacent to the recording apparatus (Synamps, Neuroscan, El Paso, TX). Subjects were seated in a slightly reclined chair with a head rest and were asked to look at the wall 3 m in front of them, keeping their eyes open and avoiding a pronounced decline of vigilance. No strict fixation was demanded. Evoked responses were recorded with 32 electrodes referred to Cz. Pure sinus tones (1000 Hz, 40 msec duration with 10 msec rise- and 10 msec fall time, interstimulus interval randomized between 1800 and 2200 msec) of five intensities (79, 87.5, 96, 104.5, 113 dB sound pressure level, generated by a PC-stimulator with Creative Labs Soundblaster 16) were presented binaurally in a pseudorandomized form by audiometry headphones. Based on the known and stable transducer sensitivity of the headphones, calibration was performed by electrical AC voltage measurement at the headphones' terminals. Continuous sinewave tones of 1000 Hz and 2000 Hz were used in the process. Stimulus levels given in this publication are the absolute sound pressure levels of a continuous sinewave, with a peak to peak amplitude equalling that of the referring stimulus. Data were collected with a sampling rate of 250 Hz and an analog bandpass filter (0.16–50 Hz). Prestimulus periods (350 msec) and poststimulus periods (800 msec) were evaluated for 100 sweeps of every intensity (all together 500 sweeps). Before averaging, the first five sweeps were excluded to reduce short-term habituation effects. For artifact suppression, all trials were

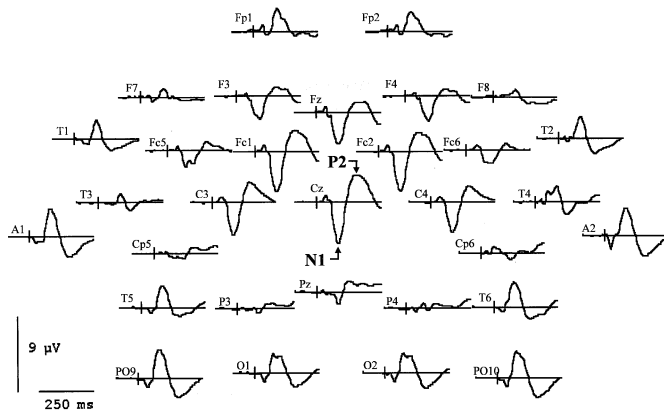


Figure 2. Evoked responses of all 31 patients and all intensities (grand average; average reference). The most pronounced amplitudes of the N1/P2-component can be observed at fronto-central electrodes as well as basal electrodes (inverse polarity).

automatically excluded from averaging, if the voltage exceeded $\pm 100 \mu\text{V}$ in any one of the 32 channels at any time point of the averaging period. For each subject, the remaining sweeps were averaged separately for the five stimulus intensities. A significant difference of accepted sweeps/intensity (maximum reach 100 sweeps) was observed between healthy subjects and patients [83.33 ± 17.47 vs. 74.13 ± 18.40 ; $F(1,60) = 4.074$, $p = .048$, respectively]. To control the possible influence of the number of accepted sweeps on the LD, we included the number of accepted sweeps as a covariate in an analysis of covariance (ANCOVA; see Results).

Dipole Source Analysis

Dipole source analysis was performed with brain electrical source analysis (BESA; Scherg and Picton 1991) which decomposes the scalp-measured N1/P2-component into two dipole source activities per hemisphere. A model for the N1/P2-component was previously described for 32 channel recordings (Gallinat and Hegerl 1994). The actual model was further adapted in a grand average of 185 healthy subjects: starting from the previously described model, the orientation and localization of the tangential and radial dipoles were adapted by an iterative algorithm to reach a minimal amount of residual variance (variance not explained by the model). This procedure was performed with mirror constraints of the dipoles to reduce the degrees of freedom (Gallinat and Hegerl 1994). This entails that the localization as well as orientation of, for example, the tangential dipoles were allowed to vary only in symmetry to maintain equal changes in each hemisphere. The same constraints were made for the radial dipoles. Fitting was performed for the time range of the N1/P2-component (62–231 msec). This procedure led to a model that was very similar to the initial one. Dipoles 1 and 2 are located in the superior temporal region, have a tangential orientation, and mainly reflect the activity of the primary auditory cortex (Elberling et al 1982; Hari et al 1980). Dipoles 3 and 4 are located in the lateral temporal lobe, have a radial orientation, and mainly reflect activity of the secondary auditory cortex (Arezzo et al 1975; Celesia 1976; Gallinat and Hegerl 1994; Scherg and von Cramon 1990). Several investigations indicate that the N1- and the P2-component have different neuronal generators (Barth et al 1993; Knight et al 1980), which

might render the modeling of both components with one tangential dipole questionable. Magnetencephalographic investigations have demonstrated, however, that the P2-generator is only 5–6 mm anterior to the N1-generator, with a 180° orientation (Tiitinen et al 1999; Papanicolaou et al 1990). This configuration allows a nearly perfect modeling of both generators by one dipole. This dipole expresses the activity of both generators by polarity inversion of the dipole activity curve without losing information (Scherg and von Cramon 1990). Furthermore, the combined modeling and quantification of the N1- and P2-component has a higher retest reliability (Hegerl et al 1994) as well as a better validity with respect to the relationship to the 5-HT system (Gallinat et al 2000); however, a relationship to 5-HT was also reported when the LD was calculated only on the P2-amplitudes (Paige et al 1994). For every subject, the magnitude of the tangential and radial dipole activity was measured separately for the five stimulus intensities as N1/P2-epoch-amplitude (62–231 msec poststimulus) and expressed as root mean squared effective amplitude, nAm (Scherg and von Cramon 1990). For data analysis, the mean activity of the left and right tangential and left and right radial dipole were used. Furthermore, the peaks of the midline electrodes Fz, Cz, and Pz (referred to linked mastoids) were determined as follows: the N1-component was considered the most negative peak between 50 and 150 msec poststimulus. The P2-component was considered the most positive peak in the time interval between 100 and 250 msec.

Loudness Dependence

A LD was performed for the tangential (LD-tangential) and the radial (LD-radial) dipoles and the midline electrodes Fz (LD-Fz), Cz (LD-Cz), and Pz (LD-Pz) using a linear regression slope from stimulus intensity as independent variable to the N1/P2-amplitude (μV in electrodes and nAm in dipoles, respectively) as dependent variable.

Statistical Methods

Group differences between patients and healthy control subjects were tested by one-way analyses of variance (ANOVAs), with a

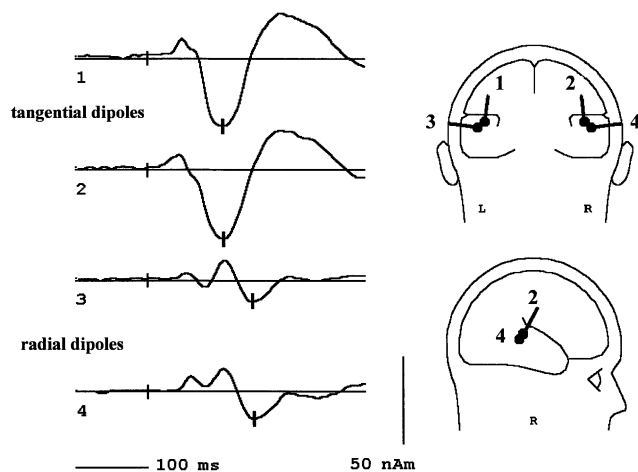


Figure 3. The dipole source model (right) of the N1/P2-component. Most of the variance of the scalp measured data in control subjects and patients is explained by this model. On the left side, the computed source activity of each dipole source for the patients with generalized anxiety disorder. The tangential dipoles (1 and 2), which are proposed to reflect the activity of the primary auditory cortex, show a dipole N1 at about 103 msec (I), whereas the radial dipoles (3 and 4) negativity occurs at about 145 msec (I).

two-tailed $\alpha = .05$. Furthermore, ANCOVAs were calculated with a two-tailed $\alpha = .05$. For the analyses of correlations, a Pearson correlation coefficient was used.

Results

STAI Scores in GAD versus Healthy Control Subjects

Patients with generalized anxiety disorder (GAD) showed a significantly higher Spielberger State Trait Anxiety Inventory (STAI) state sumscore as compared to healthy control subjects. [$F(1,56) = 55.3, p < .0001$], indicating that GAD patients had a higher “state anxiety” during the EEG recording as compared to healthy control subjects. The variable “state anxiety” was therefore included as a covariate in the further analysis.

LD in GAD versus Healthy Control Subjects

Figure 2 shows the evoked responses (N1/P2-component) to all intensities in 31 patients with GAD (grand average). Dipole source analysis reflects the activity separately for the primary and secondary auditory cortex. The activity of the corresponding tangential and radial oriented dipoles are presented in Figure 3.

For patients with GAD, a significantly shallower loudness dependence (LD)-tangential was observed compared to healthy control subjects [$F(1,60) = 6.727, p = .012$; Table 1]. The LD-radial, which is suggested to reflect activity of the secondary auditory cortex, did not differ between patients and healthy control subjects [$F(1,60) = 1.012, p = .318$]. The evoked responses as well as the dipole magnitudes in the time range of the N1/P2-component elicited by five different intensities are shown in Figures 4 and 5. With respect to the LD measured at single electrodes, patients showed a significantly shallower LD-Fz compared to healthy control subjects [$F(1,60) = 8.394, p = .005$; Figure 4], whereas the LD-Cz and LD-Pz did not differ significantly between the two groups (Table 1; Figure 5).

To test possible effects of the number of averaged sweeps and the current anxiety state on the dependent variable LD, ANCOVAs with the covariates “number of averaged sweeps” and “STAI state score” were calculated for the group comparison. Again, for patients with GAD, a significantly shallower LD-tangential was observed as compared to control subjects [$F(1,54) = 5.507, p = .023$], whereas the effects of the covariates “number of averaged sweeps” [$F(1,54) = 2.472, p = .125$] and “STAI state score” [$F(1,54) = 1.633, p = .207$] were not significant. A corresponding ANCOVA with the depending variable LD-radial showed no significant differences between GAD patients and healthy control subjects [$F(1,54) = 1.561, p = .217$]. The effects of the covariates “number of averaged sweeps” [$F(1,54) = .083, p = .774$] and “STAI state score” [$F(1,54) = .158, p = .217$] were also not significant.

Table 1. Loudness Dependence of the Auditory Evoked N1/P2-Component in Patients with Generalized Anxiety Disorder and in Healthy Control Subjects

	LD Tangential Dipole	LD Radial Dipole	LD Fz Electrode	LD Cz Electrode	LD Pz Electrode
GAD Patients	.31 ± .30 ^a	.26 ± .26	.11 ± .13 ^b	.25 ± .17	.14 ± .12
Control Subjects	.49 ± .22	.20 ± .16	.20 ± .12	.29 ± .15	.17 ± .10

n = 31 for both groups. Differences between groups, one-way analysis of variance (two-tailed).

LD, loudness dependence; GAD, generalized anxiety disorder.

^a*p* < .05

^b*p* < .01

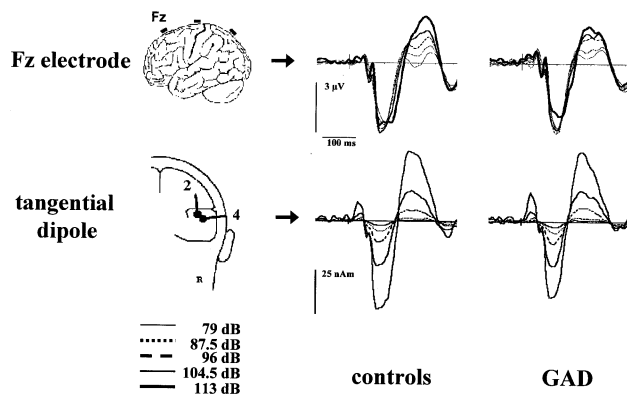


Figure 4. (Upper panel) Evoked responses (N1/P2) to five different intensities at the Fz electrode (referenced to average reference) for healthy control subjects (left) and patients with generalized anxiety disorder (GAD) (right). Note the shallow increase of the N1/P2-amplitudes with increasing intensities in GAD (especially a decrease of the N1-amplitude in response to the highest intensity). (Lower panel) Source activity of the right tangential dipole (2) in response to the five intensities for both groups. Patients with GAD (right) have a more shallow dipole activity increase as compared to control subjects. The dipole source activities are computed from the activity of 32 channels.

LD and Clinical Parameters

No significant correlation between the LD of the tangential or radial dipole sources and the Clinical Global Impression, Hamilton Anxiety Scale score, or the STAI state self-rating was observed (Table 2).

Discussion

A significantly decreased LD was found in patients with GAD as compared to healthy control subjects. This was

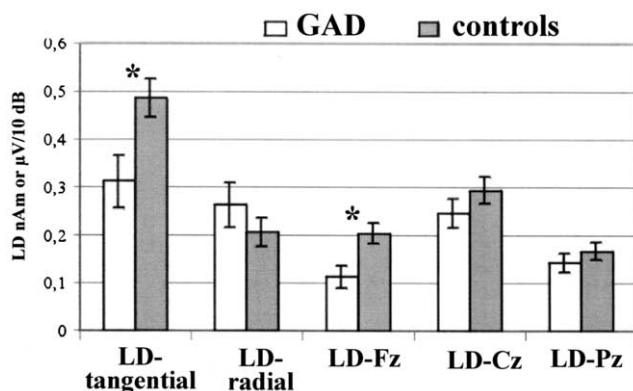


Figure 5. Mean values and SEM for the loudness dependence (LD) of the tangential and radial dipole and for the Fz-, Cz- and Pz-electrode. Significant shallower LDs for generalized anxiety disorder patients as compared to healthy control subjects were found for the LD-tangential and LD-Fz.

Table 2. Correlations (Pearson) between the Loudness Dependence of the Auditory Evoked N1/P2-Component and Clinical Parameters in Patients with Generalized Anxiety Disorder and in Healthy Control Subjects

		LD Tangential Dipole		LD Radial Dipole	
		r	p	r	p
Patients with GAD (n = 31)	Clinical Global Impression	.024	.898	-.015	.939
	Hamilton Anxiety Score	.196	.300	-.108	.571
	Spielberger Anxiety Inventory	.271	.140	-.014	.941
Healthy Control Subjects (n = 29)	Spielberger Anxiety Inventory	-.214	.265	-.134	.489

No significant correlations were observed. LD, loudness dependence; GAD, generalized anxiety disorder.

observed for the tangential but not for the radial dipole activity. As the former source reflects mainly the activity of the primary auditory cortex (Elberling et al 1982; Hari et al 1980), the result indicates an altered early auditory signal processing in GAD patients. The results agree with current concepts, which assume that the exteroceptive sensory system constitutes the afferent arm of an anxiety circuit (Charney and Deutch 1996; Coplan and Lydiard 1998). This afferent pathway is postulated to mediate sensory and situational stimuli, which are relayed from primary sensory cortex to higher cortical association areas and from there to the amygdala. The reduced LD of the tangential dipoles provides evidence that GAD is associated with a disturbed exteroceptive sensory system, occurring at the level of the first neocortical area of the ascending auditory pathway.

Altered signal processing as expressed by a reduced LD has been assumed to be a consequence of a hypothetical central mechanism regulating the sensory sensitivity (Buchsbaum 1976; von Knorring et al 1978). According to this hypothesis, a shallow LD (“reducing”) reflects a pronounced activity of a central mechanism protecting the organism from sensory overload, whereas a steep LD (“augmenting”) reflects the lack of such a protection. Following this concept, the shallow LD in patients with GAD would indicate an overactivity of this regulating mechanism. Several authors have suggested that such a mechanism acts at the level of the brainstem (Bruneau et al 1993; Lukas and Siegel 1977; Zuckerman et al 1974) and is most likely represented by the 5-HT system. Serotonin has a homeostatic function in the central nervous system (Foote and Morrison 1987; Jacobs 1990) and acts to adjust and control gain factors and excitability levels of cortical neurons (Jacobs and Azmitia 1992). The primary sensory cortices, in particular layer IV of the primary auditory cortex, contain a dense serotonergic

innervation (Campbell et al 1987; Lewis et al 1986). Layer IV also receives most of the specific thalamic sensory input (Pandya and Rosene 1993; Zilles 1990). Therefore it has been proposed that serotonergic projections from the brainstem modulate the initial signal processing in the cortex (Morrison et al 1982). In line with this, a relationship between the firing rate of serotonergic neurons in dorsal raphe nucleus and the LD measured over the primary auditory cortex in behaving cats has been found: a shallow LD was reported to be associated with a high firing rate of nucleus raphe neurons and vice versa (Juckel et al 1999). In this context, the reduced LD-tangential in patients with GAD, reflecting the activity of the primary auditory cortex, may be interpreted as a consequence of an enhanced neuronal firing of the serotonergic neurons in the dorsal raphe nucleus. With respect to other anxiety spectrum disorders, one study reported a shallow LD in patients with posttraumatic stress disorder as compared to control subjects (Paige et al 1990), compatible with the results of the current investigation.

The lack of a relationship between the LD and the current psychopathology in patients (score of the Hamilton Anxiety Scale and Clinical Global Impression) argues for a more trait-like character of the LD. This is compatible with the observation that serotonergic neurons of the dorsal raphe nucleus, in contrast to, for example, noradrenergic neurons, are characterized by a very regular and stable discharge. This discharge seems to be less influenced by external or internal changes of the organism (Aghajanian and Vandermaelen 1982; Jacobs and Azmitia 1992); however, psychological factors like attention may also influence the present group differences in LD. Some authors have reported a relationship between the LD and attentional processing (Lukas and Mullins 1985), whereas others failed to observe such effects (Orlebeke et al 1984). A methodological investigation of the effects of attention on LD showed that attention influences LD only in the low intensity range (up to 50 dB) but not at the higher intensity levels employed in our investigation (Baribeau and Laurent 1987). Although another study found effects of attention on evoked responses to higher intensities, it was stressed that group differences between augmenters and reducers were still maintained across attentional conditions (Schechter and Buchsbaum 1973). These results indicate that LD is relatively robust with respect to attentional modulation, especially for higher stimulus intensities. In line with this result, a high retest stability of the LD-tangential ($r = .91$) was found, indicating that LD is influenced rather by trait than by state variables (Gallinat and Hegerl 1994). Therefore, it seems unlikely that the group differences between GAD patients and healthy control subjects are due to attentional processes; however, the control of attention in research paradigms is a funda-

mental problem, and an effect of group differences in attention on LD can not be ruled out completely. Another factor that might explain the LD differences could be “state anxiety.” As expected, the “state anxiety” self-rating (STAI) prior to the EEG session was enhanced in GAD patients as compared to healthy control subjects. Therefore we examined the possible influence of the factor “state anxiety” on the LD group differences by calculating ANCOVAs. In these analyses, the LD differences between GAD patients and healthy control subjects remain constant even if the influence of the “state anxiety” was controlled. This indicates that “state anxiety” does not affect the group differences of the LD.

Originally, the augmenting/reducing phenomenon, which has been mainly investigated in the visual modality, was related to behavior characteristics (Buchsbaum 1971; Zuckerman et al 1974). With respect to LD (auditory modality) several studies, though not all (Carrillo-de-la-Pena 2001; Hegerl et al 1989; Wang et al 1999), reported positive relations between LD and personality traits such as extraversion (Friedman and Meares 1979a), novelty seeking (Juckel et al 1995), and sensation seeking (Brocke et al 1999; Hegerl et al 1995; Lukas and Mullins 1985; Orlebeke et al 1984). In patients with unipolar depression, a reducing characteristic was reported for the visual (for review see Buchsbaum et al 1983) but not for the auditory modality (Gallinat et al 2000; Friedman and Meares 1979b). Brocke (2000) reported a shallower LD (P2-component) in unipolar depressive patients and a steeper slope in bipolar depressed patients as compared to healthy control subjects, indicating that the LD phenomenon is not nosologically specific; however, the basis of the LD results may rather be explained by a derangement of the 5-HT system, which has been suggested to be an important mechanism in the above-mentioned diseases and personality traits. For example, low concentrations of 5-HIAA in cerebrospinal fluid were found in subjects with high sensation seeking and high impulsivity scores (Brown and Linnoila 1990; Linnoila et al 1983; Schalling and Asberg 1985; Schalling et al 1984). Moreover, recent investigations reported increased LD in conditions associated with a low serotonergic activity as produced by long-term use of “Ecstasy” (Croft et al 2001; Tuchtenhagen et al 2000) and migraine (Siniatchkin et al 2000; Wang et al 1999), whereas an extremely shallow LD was reported in patients with a 5-HT syndrome as compared to control subjects (Hegerl et al 1998).

It is not possible, however, to deduce a specific relationship between LD and 5-HT from these studies alone. Animal investigations have addressed this question in more detail. Juckel et al (1997) reported that apomorphine decreased LD over the primary auditory cortex, indicating a dopaminergic influence via D1/D2 receptors. Others

demonstrated that only 5-HT and not dopamine depletions affect AEP-amplitudes in the time range of the N1-component in rats (Ehlers et al 1991); however, a direct dopamine modulation of the LD seems to be less likely because of the low dopaminergic innervation of sensory cortices (Berger et al 1991; Lewis et al 1987). In contrast, the cholinergic system shows a high innervation in the primary auditory cortex (Wainer and Mesulam 1990; Wallace et al 1991), which may indicate cholinergic influences on the LD. Compatible with this, the muscarinic antagonist atropine increased the LD in animal experiments (Juckel et al 1997). Neither animal studies (Juckel et al 1997) nor investigations in healthy subjects visual evoked potentials (VEP) (Buchsbaum et al 1977; von Knorring and Perris 1981) provide evidence for a noradrenergic influence on the augmenting/reducing phenomenon. Paige et al (1995) reported a favorable response of depressive patients with steep LD (P2-component) to the noradrenergic antidepressant bupropion; however, the reported patient sample was small (four responders and four nonresponders), and bupropion provides some serotonergic activity (Dong and Blier 2001). Taken together, most evidence indicates a serotonergic influence of LD, which is also compatible with a recently published animal study, in which a high correlation ($r = -.80$) between the N1/P2-amplitude and the 5-HT concentration in the auditory cortex was reported (Manjarrez et al 2001).

We therefore propose that the reduced LD-tangential in GAD patients indicates enhanced 5-HT activity rather than a derangement of other neuromodulators. This assumption is compatible with several lines of evidence from animal experiments and human studies relating anxiety behavior to an enhanced serotonergic activity (Barnes et al 1992; Briley et al 1990; Germine et al 1992). If the 5-HT system is part of the central regulating system (see above), which has been proposed to be closely related to the augmenting/reducing phenomenon (Buchsbaum 1976; von Knorring et al 1978), the enhanced serotonergic activity in GAD may be seen as a compensatory or protective element for the organism. This view is in line with the observation that anxiety symptoms in patients with GAD can be ameliorated by the treatment with SSRIs (Davidson 2001; Pollock et al 2001) which is thought to enhance serotonergic activity. This compensation may involve other neuromodulators that have been linked to the pathophysiology of anxiety disorders, such as noradrenalin (Sullivan et al 1999). It was suggested that the beneficial effect of SSRI in anxiety disorders may involve an enhancement of inhibitory serotonergic afferents of the dorsal raphe nuclei that project to the locus coeruleus (Kent et al 1998). This view is compatible with animal research that indicates an inhibitory effect of serotonergic neurons on noradrenergic neurons (Jacobs and Azmitia 1992); however, the present

data can not clearly answer the question of whether an enhanced serotonergic activity is the cause or consequence of anxiety behavior.

No significant difference was observed for the LD of the radial dipole between patients with GAD and healthy control subjects. The radial dipole source is suggested to reflect activity of secondary auditory areas (Gallinat and Hegerl 1994; Gallinat et al, in press; Scherg and von Cramon 1990) because its localization, orientation, and peak latency is in agreement with intracranially recorded activity of the secondary auditory cortex in monkeys (Arezzo et al 1975) and humans (Celesia 1976). At the transition from primary to secondary auditory cortex, a decrease in the density of serotonergic innervation was observed (Lewis et al 1986; Morrison and Foote 1986; This implies a smaller influence of serotonin in the secondary as compared to the primary auditory cortex. Therefore, under the assumption of a disturbed serotonergic neurotransmission in GAD, a non-altered LD-radial in patients with GAD was expected.

When interpreting the present results, the enormous complexity of the central serotonergic system has to be kept in mind. Already at the level of the brainstem, a functional subdivision of the 5-HT system in dorsal and median raphe nuclei with overlapping but also opposing functions can be identified (Coplan and Lydiard 1998; Grove et al 1997). Furthermore, an abnormal interplay between 5-HT and several other neurotransmitters has been reported (Connor and Davidson 1998; Coplan and Lydiard 1998); however, the LD was found to be useful in predicting the response to SSRI treatment in patients with major depression (Gallinat et al 2000) and as a biological marker of the serotonin syndrome (Hegerl et al 1998). Further research is needed to determine whether a response prediction to SSRIs is also possible in GAD. This would be helpful, for example, for the clinical decision between a therapeutic agent with serotonergic or nonserotonergic mechanism.

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