Neuropsychopharmacology (2004) 29, 639–640

www.neuropsychopharmacology.org

Letter to the Editor

Family Psychopathology and Magnitude of Reductions in Occipital Cortex GABA Levels in Panic Disorder

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Neuropsychopharmacology (2004) **29,** 639–640. doi:10.1038/sj.npp.1300374

Sir

In a previous publication (Goddard *et al*, 2001), we reported the observation of abnormally low occipital cortex total GABA levels in panic disorder (PD) (14 patients and controls pairs), as determined by spatially localized ^{1}H-MRS (Rothman *et al*, 1993). These data provided direct, *in vivo* evidence implicating brain GABA neuronal dysfunction in PD. As a follow-up to this work, we wanted to determine whether there was evidence of a relationship between the family history of psychopathology and level of cortical GABA reductions in PD. We therefore performed several *post hoc*, nonparametric analyses on the above data set, after subgrouping patients according to their family history of depressive or anxiety psychopathology.

The family history of probable mood or anxiety psychopathology in first- (9/14 pts) and second-degree (in 2/14 pts) family members was obtained by chart review, and review of the semistructured interview material (SCID, ADIS-R) (First *et al*, 1995; DiNardo *et al*, 1994). Of the relatives with anxiety disorder, three had probable generalized anxiety disorder, two post-traumatic stress disorder, three panic disorder, and one agoraphobia. One patient had separate relatives with agoraphobia and PTSD. The comparison healthy control sample utilized for the study had no lifetime or family history (in first degree relatives) of psychiatric illness by clinical assessment. The controls had been paired with the patients, retrospectively, based on sex and age, as described previously. The spectroscopy was performed on an occipital region of interest (ROI), since researchers have developed a reliable method of quantifying cortical GABA in this ROI, which has been effective in identifying cortical GABA deficits in other neuropsychiatric disorders (eg alcoholism and major depression) (Behar *et al*, 1999; Sanacora *et al*, 1999). Abnormalities in this ROI could parallel abnormalities in other cortical regions such as temporal and frontal areas, though this remains to be determined. *Post hoc*, nonparametric (Wilcoxon) statistical procedures were utilized for all analyses. The α level for all statistical analyses was set at 0.05, and all tests were two-tailed. Mean values $\pm$ SD are reported. Values reported (see Table 1) have been adjusted to reflect corrections due to a gradient upgrade (erratum/correction submitted to the Archives of General Psychiatry, 1/18/02).

Also, to assess whether low cortical GABA in PD was independent of a family history of depression, we performed a related analysis in the same study sample, comparing PD patients without a family history of depression and matched controls (eight pairs). This analysis was also significant with patients continuing to have marked reductions in cortical GABA compared to controls (patients mean $\pm$ SD cortical GABA level $= 1.16 \pm 0.30$ mmol/kg *vs* control GABA $= 1.65 \pm 0.41$ mmol/kg; W statistic $= -36.00$, $p < 0.008$).

These exploratory analyses suggest the potential contribution of family history of anxiety and depressive psychopathology to the magnitude of occipital cortex total GABA reductions observed in panic disorder. The robust cortical GABA level reduction seen in the subgroup of patients with an anxiety disorder family history did not appear to be accounted for by other clinical differences from the subgroup of patients without an anxiety family history. For example, patient variables such as medication history (the frequency of medication-naïve patients was 62% (5/8) in the anxiety family history subgroup *vs* 66% (4/6) in patients without an anxiety family history: Fisher's exact test $p = 1.00$), mean panic disorder severity scale (PDSS) total scores ($p < 0.6$), mean total Hamilton anxiety scale scores ($p < 0.9$), mean total clinician-rated anxiety scale (CRAS) scores ($p < 0.7$), and PDSS mean phobia scores

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Received 12 June 2003; revised 29 September 2003; accepted 18 November 2003
Online publication: 01 December 2003 at http://www.acnp.org/citations/Npp12010303261/default.pdf

Table 1 Occipital Cortex GABA Levels (mean ± SD) by Family History of Psychopathology

Family history status of PD patients	PD patients cortical GABA levels (mmol/kg)	Matched control subjects GABA levels (mmol/kg)	Wilcoxon statistic		Approximate effect Size[#]
			W	*P*	
Anxiety disorder** ($n=8$)	1.09 ± 0.29	1.58 ± 0.26	−36	<0.008 (<0.05)*	1.8
Panic disorder ($n=3$)	1.09 ± 0.37	1.81 ± 0.08	n/a	n/a	3.1
Nonpanic anxiety disorder ($n=5$)	1.08 ± 0.27	1.45 ± 0.23	n/a	n/a	1.5
Major depression[##] ($n=6$)	0.98 ± 0.30	1.67 ± 0.14	−21	<0.03 (<0.15)*	3.1
No family history of anxiety or depression ($n=3$)	1.31 ± 0.30	1.88 ± 0.54	n/a	n/a	1.4
Total sample ($n=14$)	1.08 ± 0.31	1.66 ± 0.32	−105	<0.0001	1.9

*Indicates Bonferroni-corrected *p* values. [#]Calculated by using an SD that was an average of the patient and control subsample SDs (Cohen, 1988). **indicates that three patients also had a family history of depression. Removal of these three cases from the analysis produced a trend level of significance ($p<0.07$). [##]indicates that three patients also had a family history of anxiety.

($p<0.4$) did not differ statistically between these groups. The data, while preliminary in nature, support the contention that the magnitude of GABA neuronal dysfunction (low cortical GABA) in panic disorder could be determined by familial and possibly genetic factors. Confirmation of this result could stimulate research into panic/anxiety vulnerability genes that code for the enzymes that are required for normal GABA metabolism. However, we caution against overinterpretation of these data, since there are significant limitations inherent in this assessment, including small subgroup size, lack of formal research assessment of family psychopathology, retrospective design, and incomplete separation of both depression and anxiety family history within our study subgroups. A particular limitation with regard to sample size was the small subgroup size of patients without a family history of mood/anxiety psychopathology ($n=3$ patient/control pairs), as this meant we were unable to perform statistical comparisons between this subgroup's data and that of family history positive subgroups. These findings point to the need for prospective, comparative, follow-up studies of cortical GABA in panic disorder, utilizing larger patient groups that are mutually exclusive and carefully delineated with respect to the type of family history. This follow-up work will help determine, for example, whether PD patients with a family history of PD in first-degree relatives could be a biologically meaningful subtype of PD, based on cortical GABA levels. It will also ascertain whether a family history of PD and depression independently contribute to the magnitude of cortical GABA reductions in PD, as is suggested by our data, or whether their contribution is interrelated.

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