N-acetyl aspartate concentration is correlated with severity of generalized anxiety disorder

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Introduction
This study used proton magnetic resonance spectroscopy to assess concentrations of *N*-acetyl aspartate in patients with generalized anxiety disorder (GAD).
Materials and methods
Brain metabolite resonance was measured in the left and right dorsolateral prefrontal cortex in 20 drug-naive patients with GAD and 20 age-matched and sex-matched healthy volunteers. Correlation studies were conducted between brain metabolites and scores in the Hamilton Anxiety Rating Scale and in the Taylor's Manifest Anxiety Scale.
Results
The only statistically significant difference between the patients with GAD and their matched comparison individuals was in right N-acetyl aspartate and in right N-acetyl aspartate/creatine. There were direct correlations between either right N-acetyl aspartate or N-acetyl aspartate/creatine and the scores in the Hamilton Anxiety Scale and Taylor's Manifest Anxiety Scale in patients with GAD, but not in the control group.
Conclusion
GAD is associated with asymmetric increases in the N-acetyl aspartate and N-acetyl aspartate/creatine ratio, which are directly correlated with the severity of GAD by psychometric scales.

Keywords:
coping, prefrontal cortex, psychometric scales, stress

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Introduction

Anxiety disorders, which are among the most prevalent psychiatric disorders, afflict up to 25% of the US population at some point during their life and 17% experience an anxiety disorder during a given year [1,2]. Moreover, a recent and large study by the Mental Health in General Population database found that the overall prevalence of anxiety disorders was estimated to be 21.6%, with generalized anxiety disorder (GAD) being the most prevalent one (12.8%) [3]. In contrast, epidemiological studies are quite rare in the Arab world [4].

GAD is a disorder characterized by continuous symptoms of anxiety and vegetative hyperarousal associated with extreme and exaggerated sorrows. Sorrows may be about family harm, financial, or occupational issues. Patients are aware that their fear is not realistic and that their sorrows are exaggerated [5].

There has been an enormous increase in studies on anxiety disorders implying neuroimaging procedures [6], leading to growing evidence that brain areas involved in the stress response, including the prefrontal cortex [5,7–12], hippocampus, and amygdale [10], play a role in the symptoms of anxiety.

The dorsolateral prefrontal cortex (DLPC), together with other connected areas, is assumed to be important in working memory and in executive function, including the regulation of thinking and action. Damage to this region might impede commitment in relationships, as manifested by performance on working memory tasks, and might be associated with impaired self-efficacy, which in turn can compromise commitment [13]. It is also involved in learning how two events are associated with each other and how individuals might compare [14] or contrast these items. The right DLPC is especially likely to be involved in the memory of information that is personally meaningful. For example, when this area is anesthetized, individuals cannot readily identify a picture of their own face [15]. In contrast, the DLPC is involved in both risky and moral decisions. For example, when individuals need to decide how to distribute limited resources, representing a moral decision, the DLPC is activated. Also, this region is especially active when the costs and benefits of each alternative are weighed [16] and so it has an important role in facing stress and in managing it. Patients with major depressive disorder show low levels of activity in the left DLPC but elevated activity in the right one in response to emotional judgments. However, the elevated levels in the right DLPC transpired only when the emotional stimuli were expected [17], indicating that this region might be associated with emotional appraisal. Furthermore, in a study by Monk *et al.* [18], it was found that patients with GAD manifested greater right prefrontal cortex activation to trials containing angry faces. Moreover, Etkin *et al.* [10] found that activity in

dorsomedial and DLPC reflects the amount of emotional conflict, when a coping strategy seems not to be directly available. Engel *et al.* [5] found an increased cerebral blood flow in the right DLPC in a state of anticipatory anxiety before public speaking.

Magnetic resonance spectroscopy (MRS) use in anxiety disorders is still modest, particularly social phobia and generalized anxiety [19]. To our knowledge very few proton MRS (^{1}H-MRS) studies [7,20] of GAD have been reported. The hypothesis at the beginning of this study was that N-acetyl aspartate (NAA)/creatine ratios in DLPC is increased and may be or may not be correlated to the severity of anxiety as measured by psychometric tests. This study was approved by the Scientific and Ethics Committee of Mansoura Faculty of Medicine (Egypt).

Materials and methods

Twenty adult patients with Diagnostic and Statistical Manual of psychiatric disorders 4th edition GAD [nine men and 11 women; mean age = 35.43 years, standard deviation (SD) = 6.33] and 20 healthy volunteers (mean age = 35.27 years, SD = 7.58) were recruited through the Mansoura University Hospital Outpatient Psychiatric Clinic,. Healthy volunteers (relatives of patients in the Medicine Outpatient Clinic in the same hospital, negative family history of any psychiatric disorders, no family relationship to these study patients) were prospectively pair-matched with respect to age and sex (Table 1). Exclusion criteria included all other psychiatric disorders including substance abuse, significant medical or neurological disorders, mental retardation, head accident or trauma, patients with manifest congenital disorders, language or hearing difficulties, and patients with drugs or hormonal (contraceptive piles, etc.) induced GAD. Inclusion criteria required that all patients should be drug naive. Healthy participants had no history of axis I disorder, either personally or in first degree relatives. All participants had unremarkable urine toxicology, urine analysis, complete blood count, blood chemistry, and electrocardiography results. Timing of scans in female participants was matched relative to their menstrual phase (1 week after onset of menstruation). Groups did not differ in ethnic composition, educational level, intelligence quotient, height, or weight.

Table 1 Demonstrate the demographic data

	GAD		Control		Significant
	Mean	SD	Mean	SD	*P*
Age (years)	35.43	6.33	35.27	7.58	0.943
Age of onset	17.05	2.395	0	0	–
Duration of illness	8.95	4.79	0	0	–
IQ	91.35	6.74	92.24	7.47	0.692
Education (years)	11.6	1.66	12.19	2.58	0.475
Height (cm)	165.5	6.13	166.85	6.747	0.278
Weight (kg)	75.75	5.22	77.57	7.62	0.380
Hamilton Anxiety Rating Scale	21.50	4.71	1.52	2.13	0.000
Taylor's Manifest Anxiety Scale	35.50	8.53	2.28	2.93	0.000

GAD, generalized anxiety disorder; IQ, intelligence quotient; SD, standard deviation.

Patients had screening and day-of-scan scores of at least 15 in the Hamilton Anxiety Rating Scale [21] (mean = 21.5, SD = 4.7) and at least 21 on the Arabic version of Taylor's Manifest Anxiety Scale (mean = 35.5, SD = 8.5) [22,23]. Scores of healthy participants were substantially lower and did not overlap with those of patients (Hamilton Anxiety Scale mean = 1.5, SD = 2.1; Taylor's Manifest Anxiety Scale mean = 2.2, SD = 2.9). This study was approved by the Mansoura University Faculty of Medicine, Psychiatric Department; all volunteers provided written informed consent before participation.

Scans were taken using conventional magnetic resonance imaging and MRS on 1.5 T unit (Magnetom Symphony, Siemens, Version VA 12A, Wittelsbacher Platz, Munchen, Germany) using a head coil. Magnetic resonance imaging protocol using the single-voxel ^{1}H-MRS imaging sequence, including axial T1-WI [time repetition (TR)/echo time (TE) = 500–600/14–15 ms], sagittal T2-WI (TR/TE = 4450/86 ms), and coronal fluid attenuation inversion recovery image (9000/14/2500 ms), was acquired. The slice thickness was 6 mm, the matrix was 156×256, and the field of view was 230 mm.

Single-voxel ^{1}H-MRS imaging was performed using a spin-echo mode sequence (TR/TE = 1500/30). Water suppression was achieved with chemical shift selective. Two voxels ($15 \times 15 \times 15$) were placed on the right DLPC and on the left DLPC in control and patient groups (Fig. 1).

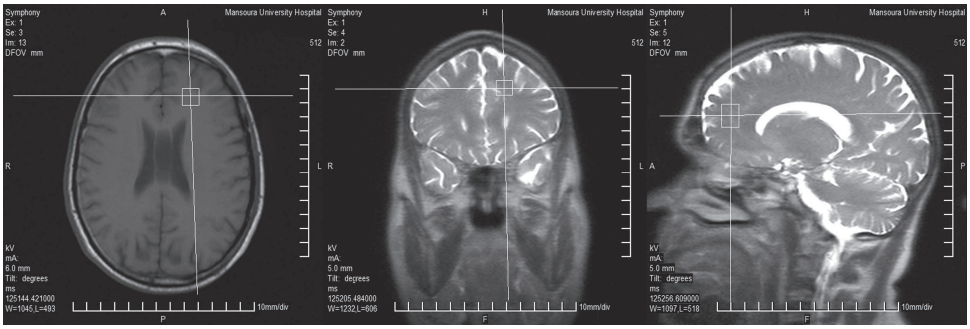
Preprocessing included the following steps: noise filtering (−2 Hz exponential multiplication) and elimination of the first three signal points to prevent artifacts in the spectrum baseline. Spectra were decomposed into major resonance and a residual. Metabolites ratios were measured by a fitting. After fitting, the spectral results were screened both by automatic analysis and by a blind manner manual inspection of eliminated bad spectral fits on the basis of poor data quality (arising because of excessive noise, patient motion, etc.). Seven spectra were rejected. In addition, ^{1}H-MRS was preprocessed to perform automatic removal of the residual water and lipid. The spectra were processed with an Hankel singular value decomposition-matched filter [24]. Signal processing was performed by time domain analysis, quantifying the resonances of interest with an iterative nonlinear method (advanced method for accurate robust and efficient spectral fitting) [25].

The raw data were transferred to an off-line workstation and were postprocessed automatically using a spectroscopic analysis package of 1.5 T (Signa; Simens, Wittelsbacher Platz, Munchen, Germany) equipped with head coil. The metabolites were identified including NAA at 2.0 part per mint (ppm), creatine at 3.0 ppm, and choline at 3.2 ppm. The integral value of each peak was dimensionless and represented relative measurement of concentration of each metabolite. The peak ratios were calculated from the integration of the single peak including NNA/creatine, NAA/choline, and choline/creatine.

Statistical analysis

Data were summarized using mean and standard deviation (quantitative data). The statistically significant

Figure 1



Shows the localization of single-voxel magnetic resonance spectroscopy on the dorsolateral prefrontal cortex.

difference between patient and control groups was tested using the *t*-test. The correlation between psychometric scales and MRS metabolites was assessed using the Pearson's correlation test. The results were computed on an IBM compatible personal computer using Statistical Package for Social Sciences for Windows 15 (SPSS Inc., Chicago, Illinois, USA).

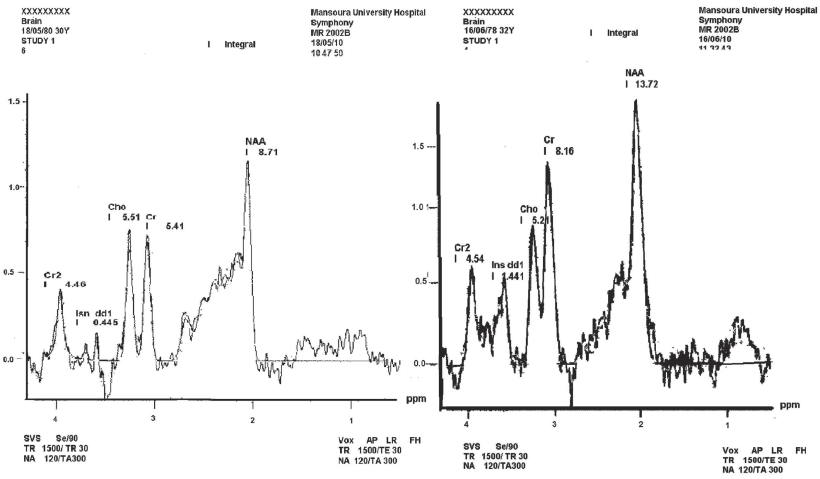
Results

The following brain metabolites were examined: N-acetyl aspartate (NAA), NAA/creatine, NAA/choline, choline, and choline/creatine in right and right DLPCs (Fig. 2). The only statistically significant differences between the patients with GAD and their matched control individuals were in right NAA (GAD, mean = 13.61, SD = ± 1.75; control, mean = 8.45, SD = ± 3.09; $P = 0.000$) and in right NAA/creatine(GAD, mean = 1.68, SD = ± 0.43; control, mean = 1.29, SD = ± 0.23; $P = 0.001$) (Table 2). The correlation study was conducted between right NAA and the score in the Hamilton Anxiety Scale and in Taylor's Manifest Anxiety Scale and between NAA/creatine and the score in the Hamilton Anxiety Scale and in Taylor's Manifest Anxiety Scale. Table 3 shows that there was a direct correlation between right NAA and the Hamilton Anxiety Scale ($r = .850$) ($P = 0.000$), right NAA and Taylor's Manifest Anxiety Scale ($r = 0.880$) ($P = 0.000$) in patients with generalized anxiety, but not in the control group (Hamilton Anxiety Scale $r = 2.64$, $P = 0.248$; Taylor $r = 0.134$, $P = 0.564$). Moreover, NAA/creatine was directly correlated with the Hamilton Anxiety Scale ($r = 0.769$, $P = 0.000$) and Taylor's Manifest Anxiety Scale ($r = 0.763$, $P = 0.000$) in patients with generalized anxiety, but not in the control group (Hamilton Anxiety Scale $r = 0.371$, $P = 0.098$; Taylor $r = 0.217$, $P = 0.345$). The correlations between the scores on anxiety scales and right NAA or right NAA/creatine ratio were also statistically significant in both sexes (Table 4).

Discussion

This study shows that there were statistically significant increases in right DLPC NAA and in right NAA/creatine,

Figure 2



Shows magnetic resonance spectroscopy spectrum curve in a control individual on the right side and the magnetic resonance spectroscopy curve of a generalized anxiety patient on the left side. Cho, choline; Cr, creatine; NAA, N-acetyl aspartate.

Table 2 Brain metabolites in control and anxiety groups

	GAD	Mean	SD	*P*
Left choline/NAA	GAD	0.47385	0.187109	638
	Control	0.44686	0.177149	
Right choline/NAA	GAD	0.39310	0.121718	625
	Control	0.41149	0.117186	
Left choline	GAD	4.41900	1.335810	784
	Control	4.29476	1.539125	
Right choline	GAD	5.11700	1.782160	0.146
	Control	4.38429	1.361652	
Left NAA	GAD	10.72850	3.113256	0.649
	Control	10.33429	2.362199	
Right NAA	GAD	13.61850	1.754916	0.000
	Control	8.45429	3.099341	
Right NAA/creatine	GAD	1.68735	0.431282	0.001
	Control	1.29171	0.233850	
Left NAA/creatine	GAD	2.26330	1.283955	0.117
	Control	1.77819	0.515117	
Left choline/creatine	GAD	0.58725	0.170211	0.401
	Control	0.53975	0.187404	
Right choline/ creatine	GAD	0.79315	0.612822	0.866
	Control	0.76620	0.382722	

GAD, generalized anxiety disorder; NAA, N-acetyl aspartate; SD, standard deviation.

Table 3 Describes correlation between brain metabolites and anxiety scales

			#1	#2
Control	Right NAA	Pearson's correlation	0.264	0.134
		[significant (two-tailed)]	0.248	0.564
GAD	Right NAA	Pearson's correlation	0.850[a]	0.880[a]
		[significant (two-tailed)]	0.000	0.000
Control	Right NAA/creatine	Pearson's correlation	0.371	0.217
		[significant (two-tailed)]	0.098	0.345
GAD	Right NAA/creatine	Pearson's correlation	0.769[a]	0.763[a]
		[significant (two-tailed)]	0.000	0.000

Note: #1=Hamilton Anxiety Scale; #2=Taylor's Manifest Anxiety Scale.
GAD, generalized anxiety disorder; NAA, N-acetyl aspartate; SD, standard deviation.
[a]Correlation is significant at the 0.01 level (two-tailed).

a measure of neuronal viability, in patients with GAD than in the control group. This increase in concentration was directly correlated with the severity of anxiety symptoms as measured by the Hamilton Anxiety Scale and the Taylor's Manifest Anxiety Scale.

The neurobiological bases of GAD are poorly characterized. Hypermetabolism in prefrontal cortical regions [26] and neuronal hypertrophy in limbic structures [27] have been observed. ^{1}H-MRS studies in related disorders have found topographic reductions (or no change) in prefrontal cortical or hippocampal measures of NAA, an amino acid considered as a marker of neuronal viability [28]. Similarly, decreases in NAA/creatine ratios were found in prefrontal cortical regions of adult nonhuman primates who had undergone adverse rearing conditions as infants approximately 10 years earlier, suggesting possible trauma-related neurotoxicity [29].

The results of this study are consistent with Mathew *et al.* [7], who recently described that patients with GAD had a 16.5% higher NAA/creatine ratio, a suggested marker of neuronal viability, in right DLPC compared with healthy controls.

The increase in NAA and NAA/creatine ratio could reflect an increase in the number of neurons in DLPC. This increase in number of neurons may be an adaptive mechanism to stress, which needs further studies to confirm this assumption. The direction of NAA/creatine abnormality in GAD is potentially consistent with findings suggesting prefrontal cortical hypermetabolism in GAD [26] and increased cerebral blood flow in the right DLPC in persons with social phobia anticipating public speaking [30].

The adaptive mechanism to stress could be explained as follows; there are evidences to suggest that the developing brain organizes in response to the pattern, intensity, and nature of sensory perceptual and affective experience of events during childhood [31,32]. Therefore, stress

Table 4 Illustrates correlation between brain metabolites and scores on anxiety scales according to sex

		Control				GAD			
Sex	Brain metabolites/anxiety scales score	Mean	SD	*R*	Significant	Mean	SD	*R*	Significant
Male	Right NAA	8.43	3.20	0.273	0.345	14.28	1.90	0.800[b]	0.002
	Hamilton Anxiety Scale	1.28	1.72			23.75	4.45		
	Right NAA	8.43500	3.20	−0.113	0.701	14.28	1.90	0.858[b]	0.000
	Taylor's Manifest Anxiety Scale	2.5000	2.90			39.83	7.56		
	Right NAA/creatine	1.29557	0.25	0.402	0.154	1.87	0.37	0.637[a]	0.026
	Taylor's Manifest Anxiety Scale	2.5000	2.90			39.83	7.56		
	Right NAA/creatine	1.29557	0.25	0.611	0.107	1.87	0.37	0.698a	012
	Hamilton Anxiety Scale	1.2857	1.72			23.75	4.45		
Female	Right NAA	8.49	3.11	0.27	0.54	12.61	0.85	0.842[b]	0.009
	Hamilton Anxiety Scale	2.0	2.88			18.12	2.74		
	Right NAA	8.49	3.11	0.197	0.673	12.61	0.85	0.873[b]	0.005
	Taylor's Manifest Anxiety Scale	1.85	3.18			29.00	5.20		
	Right NAA/creatine	1.28400	0.20	−0.225	0.628	1.40	0.36	686[a]	0.040
	Taylor's Manifest Anxiety Scale	1.8571	3.18			29.00	5.20		
	Right NAA/creatine	1.28400	0.20	0.303	508	1.40	0.367	0.850[b]	0.000
	Hamilton Anxiety Scale	2.0000	2.88			18.12	2.74		

GAD, generalized anxiety disorder; NAA, N-acetyl aspartate; SD, standard deviation.
[a]Correlation is significant at the 0.05 level (two-tailed).
[b]Correlation is significant at the 0.01 level (two-tailed).

responses can affect the development of the brain by altering neurogenesis, migration, synaptogenesis, and neurochemical differentiation [33,31]. Hence, the brains of traumatized children develop to be hypervigilant and are potentially related to threat. These children are in a persistent state of arousal, and therefore experience persistent anxiety [33]. Other studies suggest that early exposure to consistent, daily stress can later result in more adaptive behavior and resiliency, whereas exposure to unpredictable stress can result in deficits. Predictability and control can make events much less destructive or traumatic [34]. Although these adaptive changes in the brain make a child better suited to sense, to perceive, and to act on threats in their world, these 'survival tactics' ill-serve the child when the environment changes (e.g. in school, peer relationships) [34].

A similar condition is described by Whiteside *et al.* [35] who observed higher glutamate + glutamine/creatine and NAA/creatine in the orbitofrontal cortex of patients with obsessive compulsive disorder. The investigators suggested that this increase in NAA could reflect an increase in the number of neurons, which is consistent with neurobiological models of obsessive compulsive disorder that have postulated higher activity in the cortex or with neurodevelopmental theories involving inefficient neuronal pruning in this disorder.

In contrast, the scores in Taylor's Manifest Anxiety Scale and in the Hamilton Anxiety Scale, which examine the severity of anxiety, were directly correlated to right NAA and NAA/creatine. This means that the severe the anxiety the more the need for neuronal activity to compensate it and to prepare the individual to combat the stress. Hence, an increase in NAA, which is a neuronal viability marker, is observed. This may also support this study assumption that there may be an adaptive way for the brain to face stress that appeared clinically as GAD. This study may open new areas for research on the adaptive function of brain to stress according its severity. In addition, it also puts forth some questions for further studies 'Is the brain of a patient with GAD not same for all patients depending on the degree of stress each one faces? And if it is true, is it wise to have the same treatment for all patients?'

Conclusion

This study found that there were increases in right DLPC NAA and right NAA/creatine in patients with GAD than in the control group. These increases in concentrations were directly correlated with the severity of anxiety symptoms. From this finding, an assumption can be made that there may be a special way of adaption to stress and GAD may be present. Further studies are needed to confirm or to refuse this assumption.

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الآلية التكيفية لاضطراب القلق العام: دراسة بواسطة الرنين المغنطيسي الطيفي

المقدمة: استعملت الدراسة الحاليةُ بروتون الرنينُ المغناطيسي الطيفي لقياس تركيز إن أسيتيل اسبرتات في مرضى القلق العام. **الطريقة:** تم قياس طيف التمثيل الايضي للمخ في الجانبين الأيمن و الأيسر من الفص الأمامي الخلف جانبي للمخ في 20 من المرض بالقلق العام الذين لم يسبق أن تعاطوا أدوية نفسية سابقا و مثلهم مجموعة مقارنة من الأصحاء. كما تم إجراء دراسة ارتباط بين تركيز ناتج التمثيل الايضي للمخ و درجة القلق علي مقياس هاماليتون و علي تيلور للقلق الظاهر. **النتيجة:** لم يتبين وجود أي اختلاف ذو دلالة إحصائية بين ناتج التمثيل الايضي للمخ للمرضي و الأصحاء معدا بالنسبة ان استيل اسبرتات علي الفص الأيمن للمخ و كان هناك ارتباط ذو دلالة إحصائية بين هذه الزيادة و القياس علي مقياس هامليتون للقلق و مقياس تيلور للقلق الظاهر. **الاستنتاجات:** اضطراب القلق الْعامّ يتميز بزيادة غير مُتناظِرةٍ في تركيز إن أسيتيل اسبرتات و نسبة إن أسيتيل علي كرياتين مع وجود علاقة ارتباط طردية بينهما و شدَّةِ اضطراب القلق العام الذي يمكن تفسيرة كنوع من الآلياتً التكيفية لمواجه الضغوط النفسية.