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SCIENTIFIC CORRESPONDENCE

Dissociating anxiety from pain: mapping the neuronal marker N-acetyl aspartate to perception distinguishes closely interrelated characteristics of chronic pain

SIR – The notion that human cognitive-perceptual states are a reflection of brain chemistry is a fundamental assumption in neuroscience. However, a direct correspondence between these two domains has not been shown. Here we demonstrate distinct mappings between brain chemistry and cognitive-perceptual properties of chronic pain. By examining brain regional variations of the neuronal marker N-acetyl aspartate (NAA), we identify distinct relationships between regional variations in brain NAA and the characteristics of pain and of anxiety from which such chronic back pain patients suffer.

Most studies of pain, especially regarding chronic pain, agree that anxiety and pain are interrelated. However, the neurobiology of their relationship remains unknown, and there is no knowledge about the brain regions that may distinguish between them. We used proton magnetic resonance spectroscopy (^{1}H-MRS) to measure levels of NAA (the dominant peak in ^{1}H-MR spectra) in multiple brain regions,[1] and correlated these levels with perceptual measures of pain as identified by the short form of the McGill Pain Questionnaire (SF-MPQ)[2] and with perceptual measures of anxiety as measured by the State-Trait Anxiety Inventory (STAI).[3] We analyzed these relationships in chronic back pain patients ($n = 9$, mean age = 45 ± 6 years) and in age- and sex-matched healthy volunteers ($n = 16$, mean age = 44 ± 3 years), where ^{1}H-MRS measures were done in the orbital frontal cortex (OFC), cingulate, dorsolateral prefrontal cortex (DLPFC) and thalamus of the left hemisphere (all subjects were right-handed).

The mapping between brain regional NAA with perceptual measures of pain in back pain patients shows

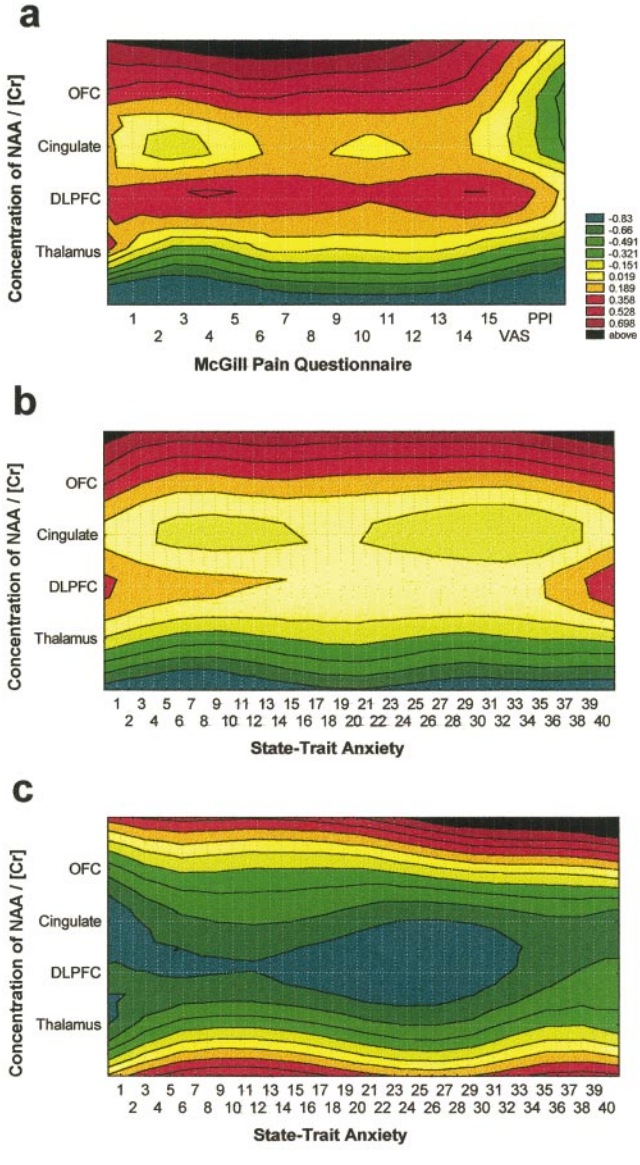

Figure 1 Mappings between brain regional variations of NAA and perceptual measures of pain and anxiety. Contour plots are shown for correlations of NAA peak (relative to Cr peak) in four left-hemispheric brain regions (OFC, cingulate, DLPFC, thalamus) with various measures of pain (a) and anxiety (b and c). Pain perception measures in chronic back pain patients are strongly related with NAA in DLPFC and OFC ($F = 26.5$, $P < 0.000002$; for correlations compared between them and the other two regions, ANOVA). Anxiety in chronic back pain (b) and in normal subjects (c) is positively related with NAA in OFC (stronger in chronic back pain, $F = 6.9$, $P < 0.01$, ANOVA). The relation between anxiety and NAA in the other three regions is also distinct between normal subjects and chronic back pain patients (cingulate $F = 4.2$, $P < 0.05$; DLPFC $F = 27.6$, $P < 10^{-7}$; thalamic NAA–anxiety relationship shifts from positive to negative with chronic back pain $F = 31.1$, $P < 10^{-7}$; regional correlations compared between the two subject groups). The measures of pain are responses to the short form of the McGill Pain Questionnaire (SF MPQ: 1 = throbbing, 2 = shooting, 3 = stabbing, 4 = sharp, 5 = cramping, 6 = gnawing, 7 = hot-burning, 8 = aching, 9 = heavy, 10 = tender, 11 = splitting, 12 = tiring-exhausting, 13 = sickening, 14 = fearful, 16 = punishing-cruel, VAS = visual analogue scale, and PPI = present pain intensity index). The measures of anxiety are responses to the State & Trait Anxiety Inventory (STAI: questions 1–20 correspond to state anxiety and 21–40 to trait anxiety). Correlation values (Pearson's correlation coefficient) are presented in color gradients as shown.

a specific pattern (Figure 1a, where correlation coefficients between brain regional NAA and perceptual measures are presented in color-coded contour plots): NAA in OFC and DLPFC are strongly positively related with the pain measures. This mapping is different for anxiety. In the same back pain patients the mapping between NAA and the measures of anxiety are positive in OFC but not in DLPFC (Figure 1b). In normal subjects, the mapping between brain regional NAA and anxiety (Figure 1c) shows a pattern different from that in the chronic pain patients: in the patients, the NAA–anxiety relationship is stronger in OFC (more positive), weaker in cingulate and DLPFC (less negative), and has switched from positive to a negative relationship in the thalamus. Therefore, in the patients, levels of NAA show a regional differential role of the frontal cortex where both OFC and DLPFC correlate with the pain of chronic pain and only OFC correlates with the anxiety of chronic pain. Moreover, NAA mapping to anxiety distinguishes between normal subjects and patients in all brain regions examined. Since normal subjects by definition have no pain, we only show their chemical-perceptual mapping for anxiety.

Previous functional brain imaging studies indicate that the prefrontal and cingulate cortices are involved in chronic pain, while the thalamus has been shown to be negatively involved in chronic pain.[4–8] Studies of hypnotic modulation of pain perception in normal subjects highlight the special role of the cingulate in the affective component of pain.[9] These studies ignore the influence of anxiety, which is a major confounder contaminating the brain circuitry identified underlying these pain states. Previous studies of anxiety disorders implicate multiple brain regions in their pathophysiology, including anterior limbic/paralimbic regions and OFC.[10] NAA in OFC was identified as the strongest chemical marker for anxiety in healthy humans.[11] Thus, in general our results, using NAA as a chemical marker, agree with the circuitry identified for both pain and anxiety. Our recent ^{1}H-MRS study indicated that the main chemical reduced in concentration in chronic pain was NAA in DLPFC.[12] Decreased brain NAA has been reported for most neurodegenerative diseases,[13] implying that NAA can be viewed as a neuronal marker. Therefore, decreased NAA in chronic pain suggests that chronic pain may be linked to neuronal loss and degeneration. The present results extend this observation by indicating that the neuronal loss occurs in a very specific manner, where the brain NAA levels reorganize across regions to distinctly reflect the dual states of heightened pain and anxiety. This process may be a result of degeneration coupled with changes in connectivity, and supply of metabolites and neurotransmitters (NAA also is a precursor of the neurotransmitter N-acetyl-aspartyl-glutamate). We have suggested earlier[12] that the mechanism underlying the localized neuronal degeneration for chronic pain may be due to the hyperactivity of the brain regions involved, since functional magnetic resonance imaging studies in our lab demonstrate prefrontal hyperactivity in chronic pain patients. The functional imaging results indicate that the prefrontal region is continuously and vigorously active in chronic pain, which may lead to local hyperactivity induced-neurodegeneration. The same mechanism may be responsible for the relationship between OFC and anxiety in chronic pain state, and this may in fact be a general mechanism that controls the extent of local, or more generalized, depletion of neurons, depending on the specifics of the brain abnormalities examined. In normal subjects the relationship between OFC and anxiety may be different, since we found no evidence for neuronal degeneration. Moreover, our studies of physiological anxiety detected increased levels of NAA in OFC,[11] which most likely suggest neuronal reorganization (ie, an increased level of NAA is associated with increase of neuronal volume, possibly due to sprouting). Correspondence between these processes was discussed in our previous report.[11]

Our results shed new light on the neurobiological mechanisms and regional brain circuitry implicated in pain and anxiety, and their interrelationship in the brain. This study is the first to outline the anatomical regions that relate pain and anxiety. Further details regarding the interrelationship between pain and anxiety await future studies. More importantly they demonstrate an intricate balance between brain chemical variations across regions where subtle shifts in the human personality can be captured by monitoring the regional chemical changes of the brain. The simplicity of this relationship is surprising although consistent with the known functional anatomy of the cortex. The reorganization of the relationship between personality and brain chemistry, from normal subjects to patients, is also consistent with the multiple demonstrations of the plasticity of the adult cortex. It should be emphasized that this study is rather preliminary since the number of patients studied is small. However, if these findings are replicated in a larger cohort and are also demonstrated for other cognitive states, the approach can become a new method for tracking the long-term brain chemical characteristics of cognition.

ID Grachev[1,2], BE Fredrickson[3], AV Apkarian[4]
[1]Department of Neurosurgery; [2]Department of Neuroscience and Physiology; [3]Department of Orthopedic Surgery, SUNY Upstate Medical University, Syracuse, New York 13210; [4]Department of Physiology, Northwestern University Medical School, Chicago, IL 60611, USA

Correspondence should be addressed to ID Grachev. E-mail: grachevi@mail.upstate.edu

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Possible influence of the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene on therapeutic outcome in affective disorders

SIR – The insertion (I)/deletion (D) polymorphism of the angiotensin I-converting enzyme (ACE) gene seems to influence therapeutic outcome in patients suffering from unipolar major depression.

ACE is involved in blood pressure regulation via the renin-angiotensin-cascade. It is also expressed in the central nervous system, where its primary function comprises degradation of neuropeptides including substance P (SP). Because of the possible antidepressant effects of SP antagonists,[1] and the decrease of cerebral SP content after monoamine reuptake inhibitors,[2,3] the influence of SP on both pathophysiology and the relief of depression has been hypothesized repeatedly.[4]

About 50% of the interindividual variability of ACE concentration is determined by an I/D-polymorphism[5,6] in the ACE gene. Since the D-allele was associated with higher ACE levels[7] and higher neuropeptide degradation capabilities, this might influence therapeutic efficacy. Moreover, an association between the D/D-genotype and affective disorders was found in Japanese patients.[8] The present study investigated whether this finding could be replicated in European patients and whether the ACE gene variants might have any impact on the outcome of antidepressive therapies.

Ninety-nine unrelated patients with unipolar major depression (DSM-IV) and 99 age- and sex-matched healthy controls from the general population were investigated. All study participants were Caucasians from southern Germany. Controls were screened for psychiatric disorders (Structured Clinical Interview for DSM-IV) and familial loading (SADS Family History form) to exclude those with first degree affected members. Psychiatric ratings in patients included the Hamilton rating scale for depression (HAM-D17) and the clinical global impression scale (CGI, Item 1 - severity of disease). Patients received different treatments (n = 23 tricyclic anti-depressants, 43 mirtazapine, 12 selective serotonin reuptake inhibitors, 10 venlafaxine, 17 electroconvulsive therapy, 23 repetitive transcranial magnetic stimulation, 29 combinations). Genotyping of the I/D-polymorphism was performed according to Rigat *et al*[7] with slight modifications. Both laboratory procedures and ratings were carried out under single-blind conditions.

Categorical variables were compared using the two-sided Fisher's Exact test. We compared differences between I/I-homozygotes and D-allele carriers in numerical variables using the Student's t-test. Presup-

Table 1 Demographic, genetic and clinical characteristics of depressed patients and healthy controls

		Patients	*Controls*
n		99	99
Sex (M/F)		35/64	35/64
Age (mean ± SE)		52.3 ± 1.31	48.9 ± 1.10
Range		24–80	27–73
Psychiatric history* single/recurrent episodes		25/74	–
Age of onset (mean ± SE)		41.3 ± 1.61	–
No. of episodes		3.6 ± 0.45	–
Genotype I/I**		21.2% (n = 21)	28.2% (28)
H–W expected		20.7% (20.5)	26.5% (26.3)
Genotype I/D		48.5% (48)	46.5% (46)
H–W expected		49.5% (49.1)	50.0% (49.5)
Genotype D/D		30.3% (30)	25.3% (25)
H–W expected		29.8% (29.5)	23.5% (23.3)
Frequency Allele I		45.5%	51.5%
Frequency Allele D		54.5%	48.5%
Psychiatric ratings HAM-D17 week 4*** (mean ± SE)	I/I	22.6 ± 1.93	–
	I/D, D/D	14.6 ± 0.99	–
CGI Item 1 week 4*** (mean ± SE)	I/I	5.33 ± 0.27	–
	I/D, D/D	4.12 ± 0.15	–
Number of treatments*** (mean ± SE)	I/I	2.95 ± 0.31	–
	I/D, D/D	2.13 ± 0.12	–
Hospitalisation (days)*** (mean ± SE)	I/I	82.1 ± 13.4	–
	I/D, D/D	58.6 ± 3.63	–

*No significant differences between genotypes (χ^2 = 3.39, df = 2; P = 0.18; t-test; T = –0.44, P = 0.66).
**No significant differences between patients and controls; Genotype I/I *vs* I/D *vs* D/D: χ^2 = 1.5, df = 2; P = 0.47; Genotype I/I *vs* (I/D + D/D): Fisher's exact test, two-sided: P = 0.162;
***Significant better improvement after 4 weeks, significant less different treatment attempts and significant shorter hospitalisation times in carriers of the D-allele. HAM-D17 t-test: T = 3.72, $P < 0.0001$; CGI t-test: T = 3.69, $P < 0.0001$; number of treatments t-test: T = 2.46, P = 0.021; duration of hospitalisation t-test: T = 2.38, P = 0.020.