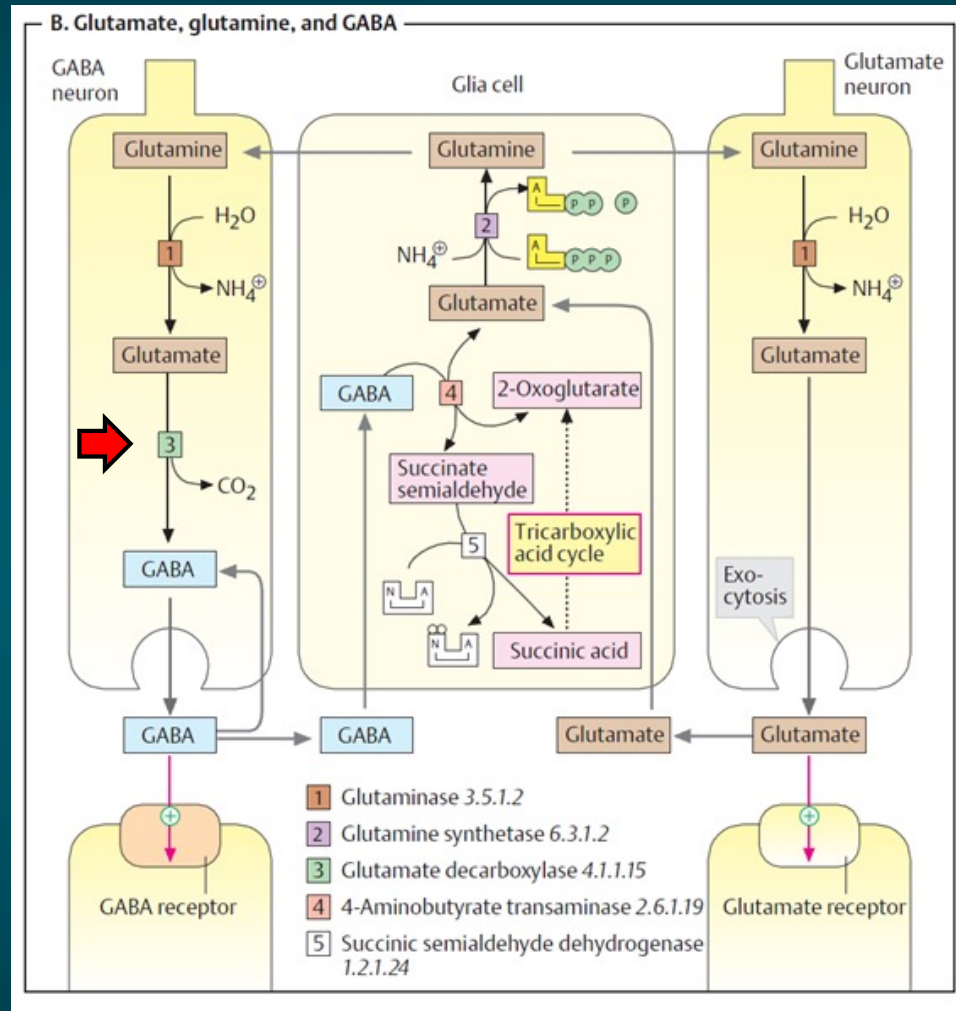


GABA magnetic resonance spectroscopy

Jan Willem van der Veen

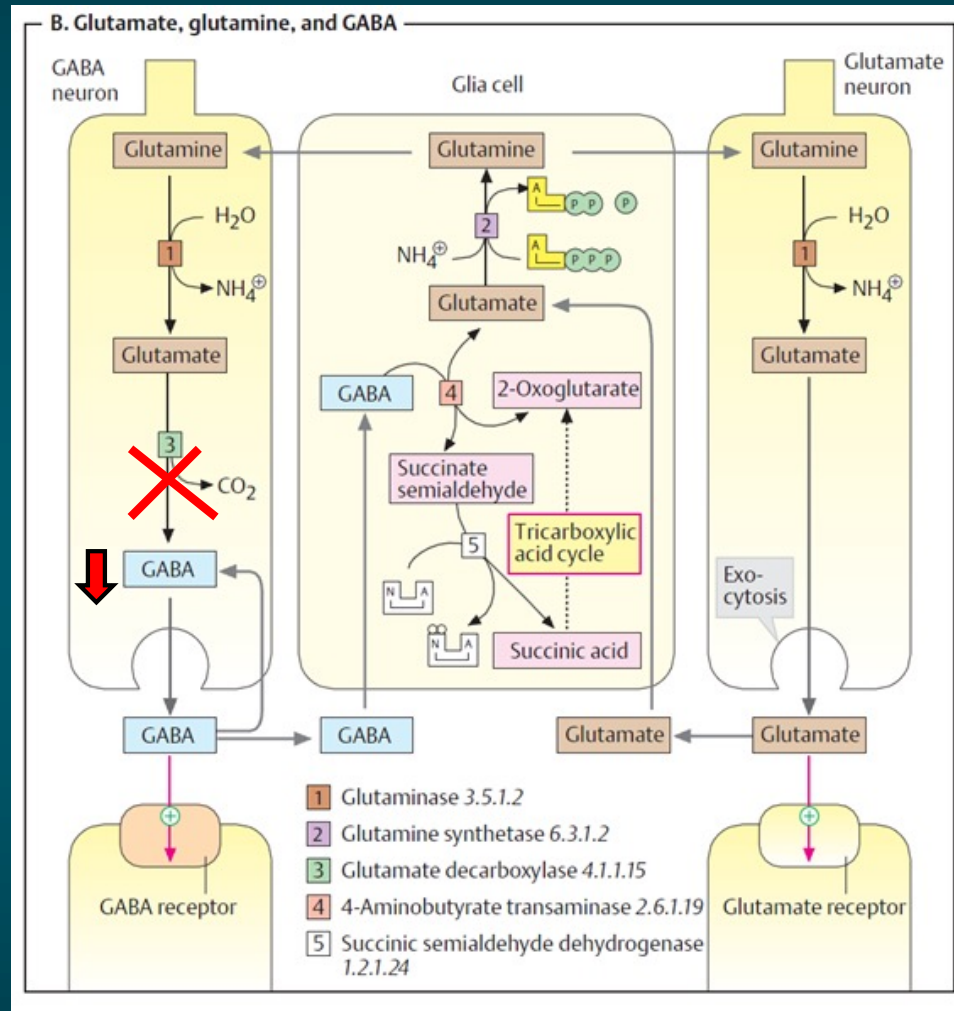
NIH, NIMH, Magnetic Resonance Spectroscopy Core, Bethesda, MD, USA

Gene GAD1 -> glutamic acid decarboxylase [3]



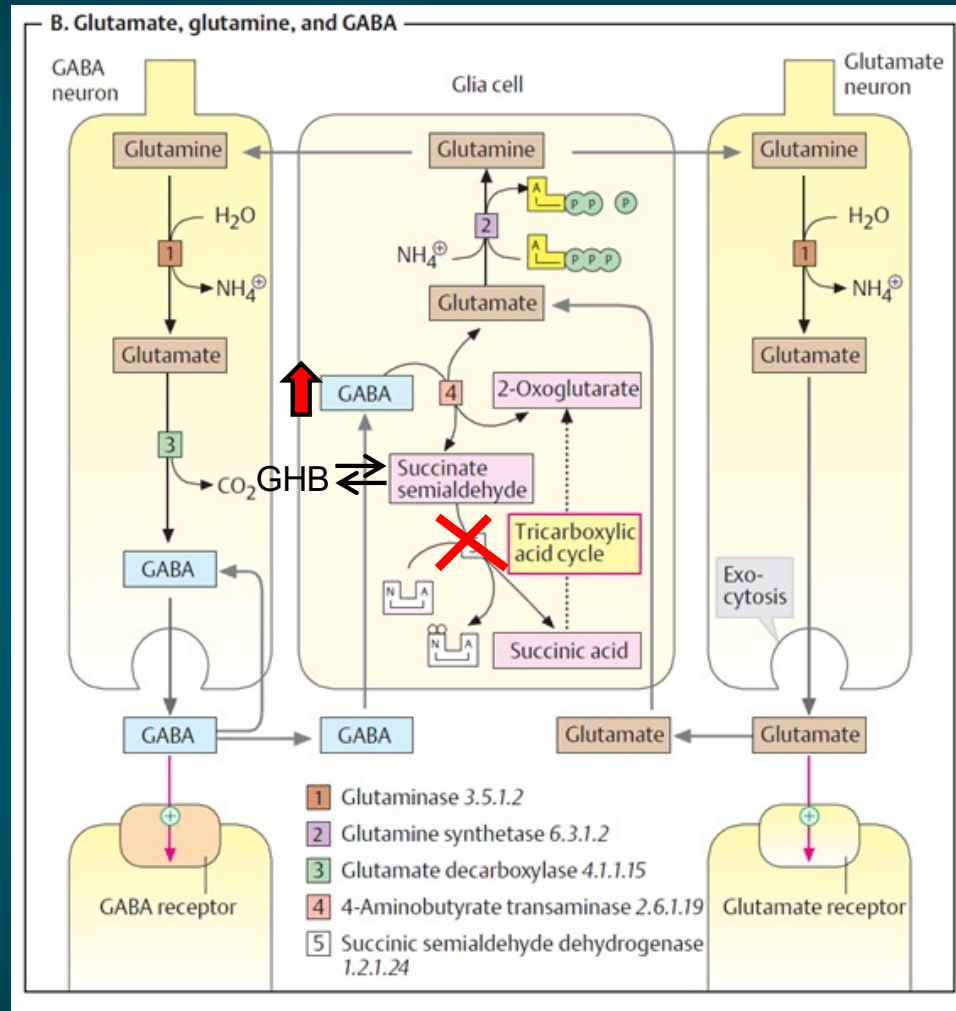
To study the effects of single nucleotide polymorphisms (SNP) in mood disorders and risk for psychosis

Stiff person syndrome (SPS)



Autoimmune disease, high level of glutamate decarboxylase antibodies

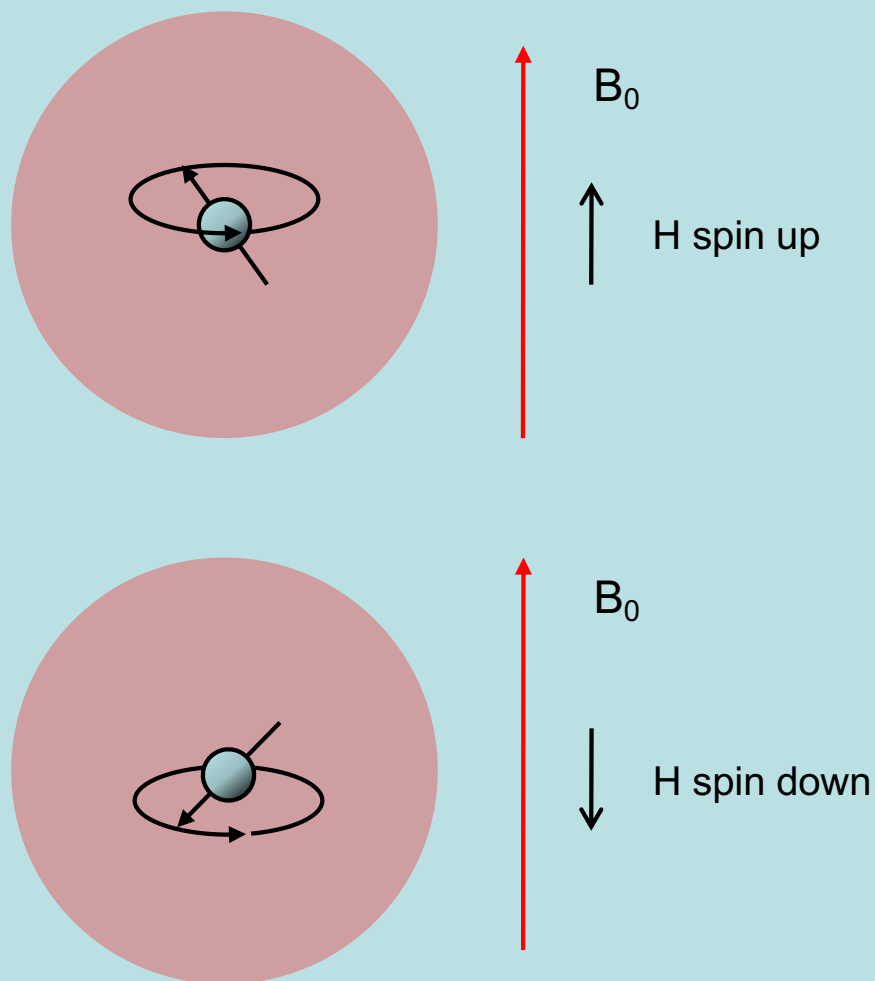
Succinic semialdehyde dehydrogenase deficiency (SSADH)



Mutations in ALDH5A1 gene encoding SSADH enzyme. Developmental delay, Mental retardation, Behavioral problems, Hypotonia, and Ataxia

Proton magnetic resonance

Quantum mechanical model of proton magnetic resonance: Quantization of the magnetic spin in two levels, spin up and down

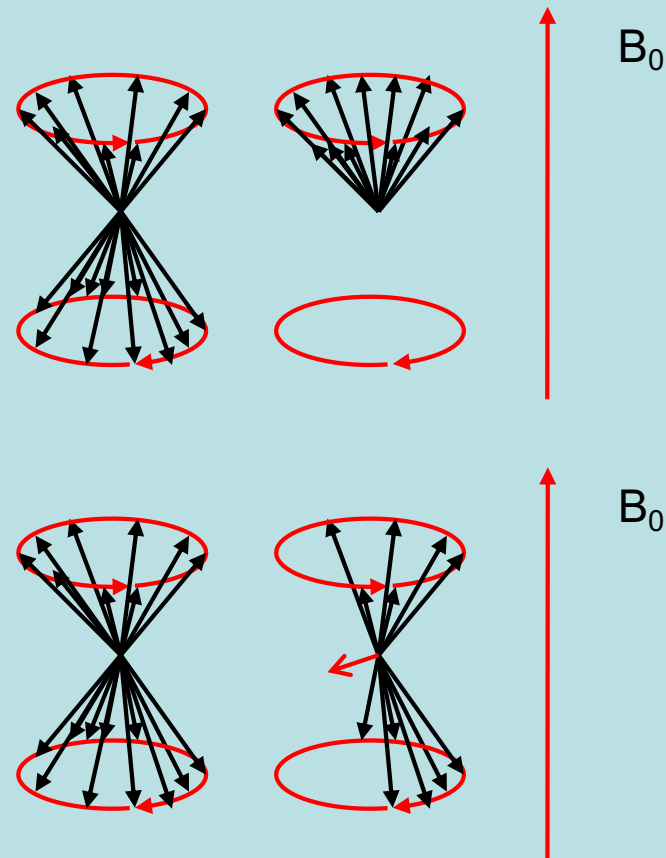


Magnetic resonance

Creating coherence in populations from the small fraction of additional spins results in a net transversal rotating magnetization

RF \longrightarrow

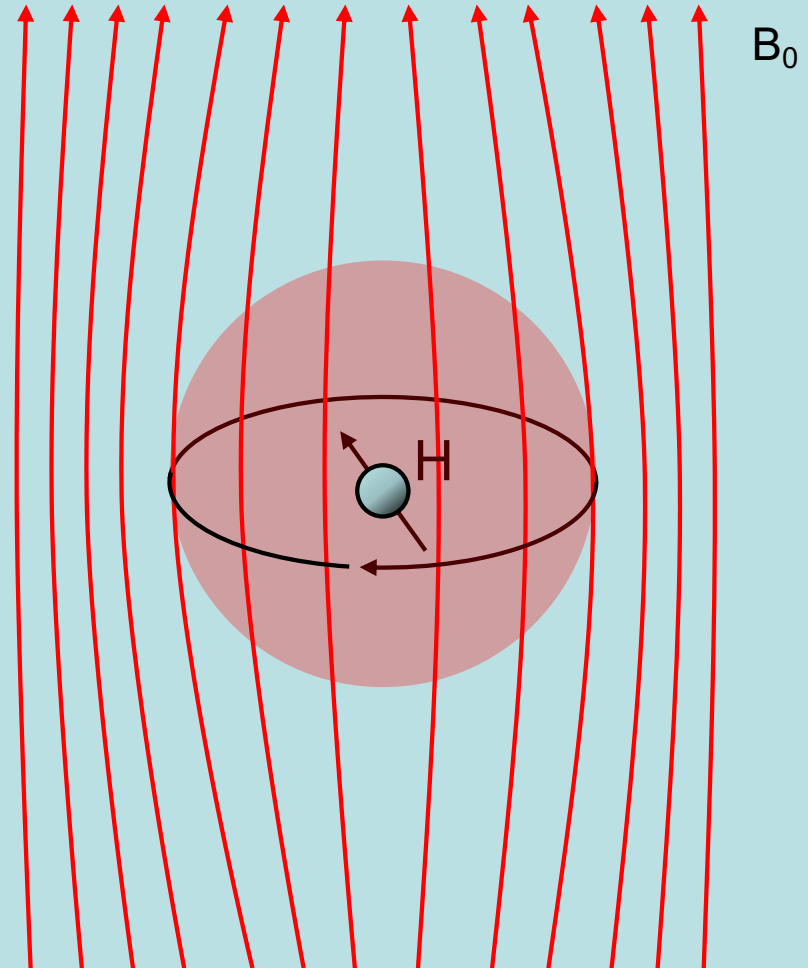
$$f = \gamma / \pi B_0$$



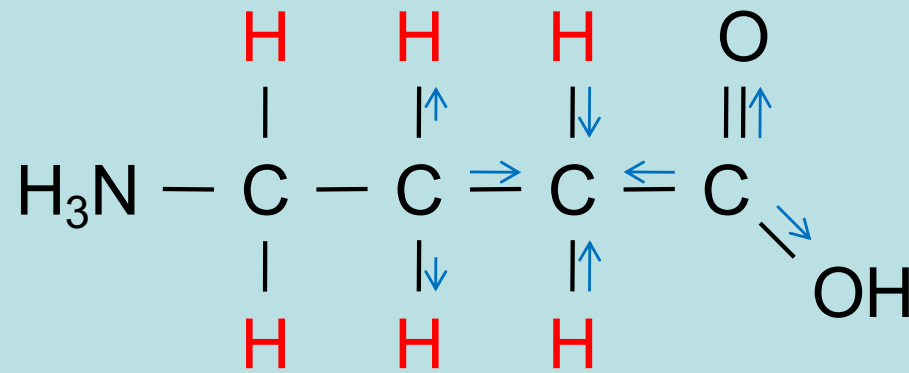
Magnetic resonance

Electron shielding of the
nuclear spin

$$f = \gamma / \pi (1 - \sigma) B_0$$



Chemical shift



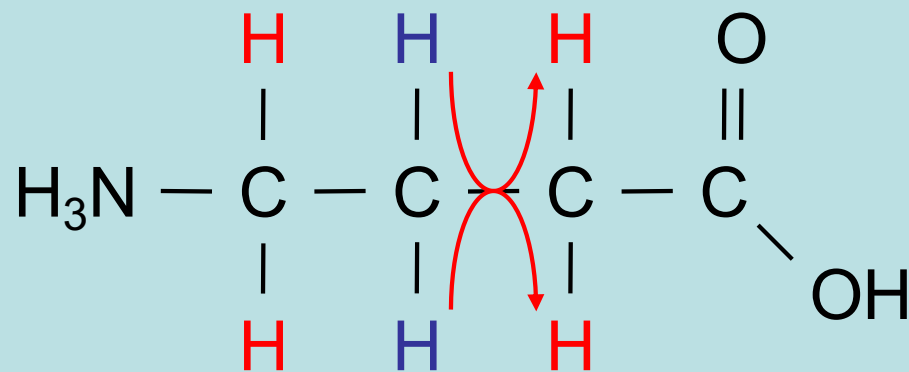
$$f = \gamma/\pi (1-\sigma) B_0$$

High field



Low field

J coupling



$$f = \gamma/\pi (1-\sigma) B_0 + J^*I$$

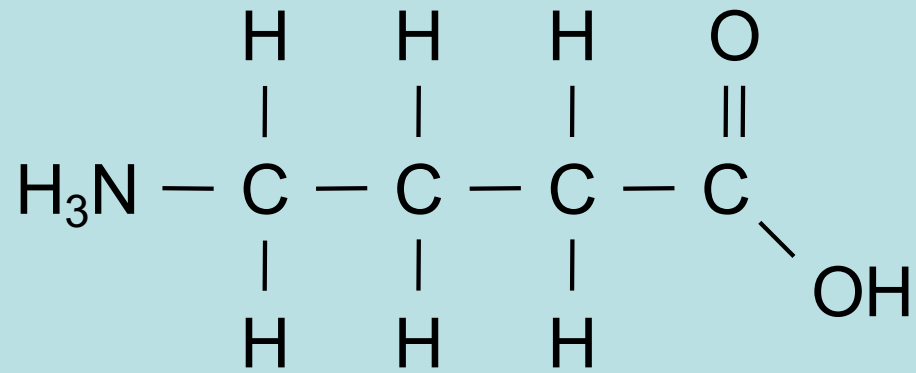
High field



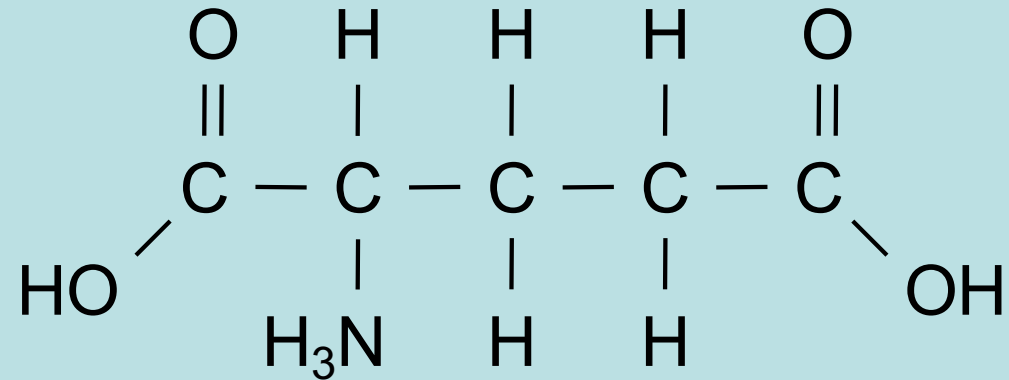
Low field

J coupling

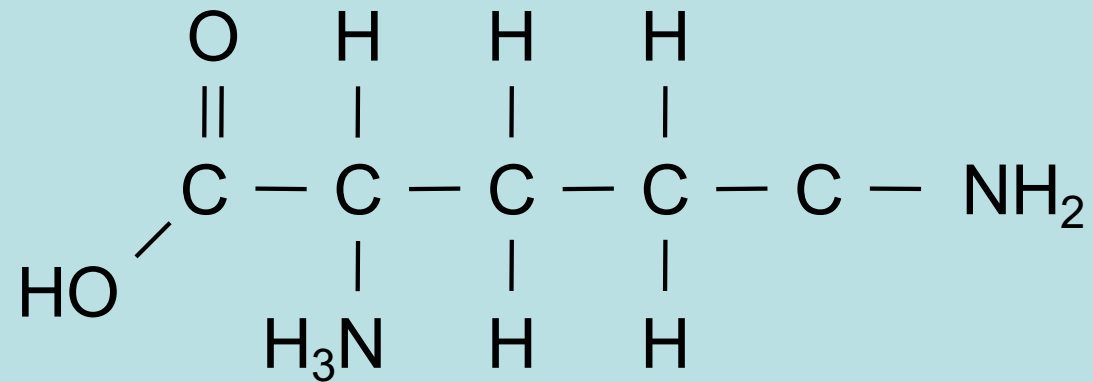
GABA



Glutamate



Glutamine



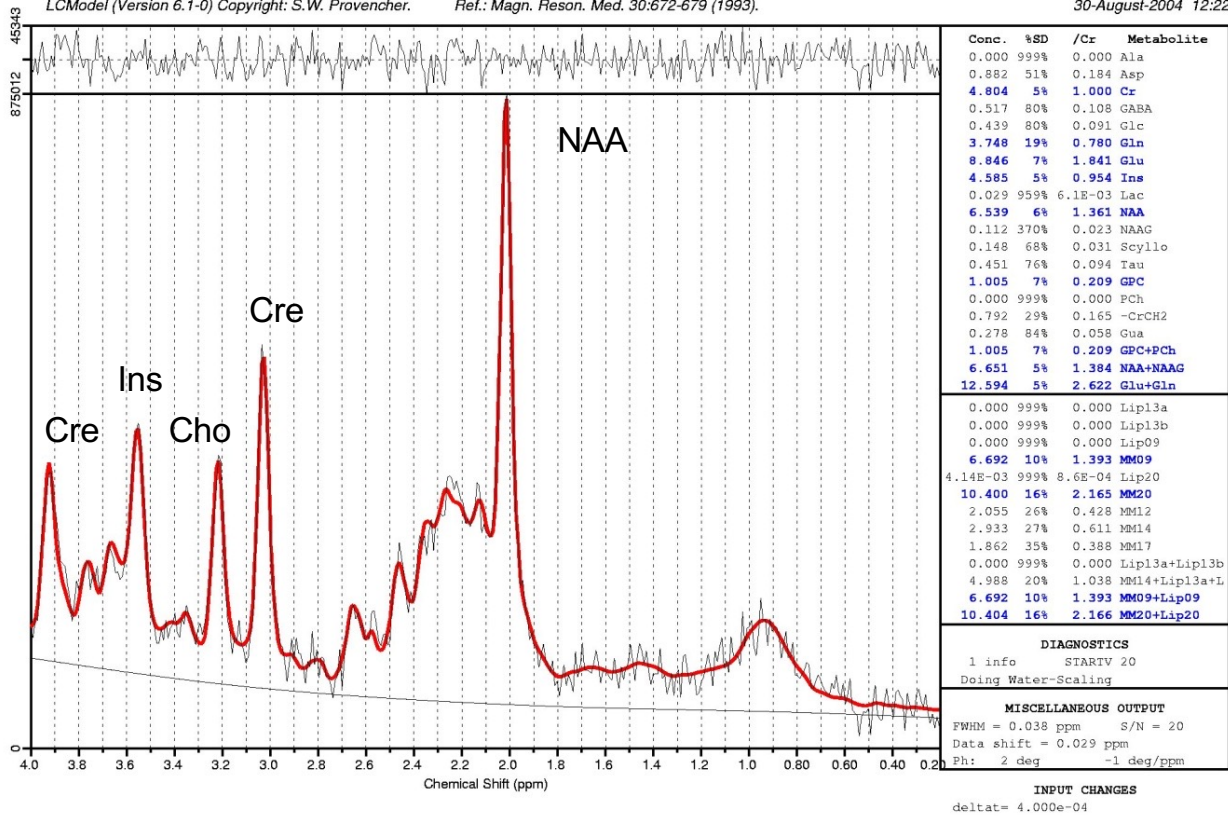
Example spectrum

Exam # ID= presscsi TE/TR/NS=30/2000/128 TG/R1/R2=153/11/30 8.0mL
(NIH INVIVO NMR)

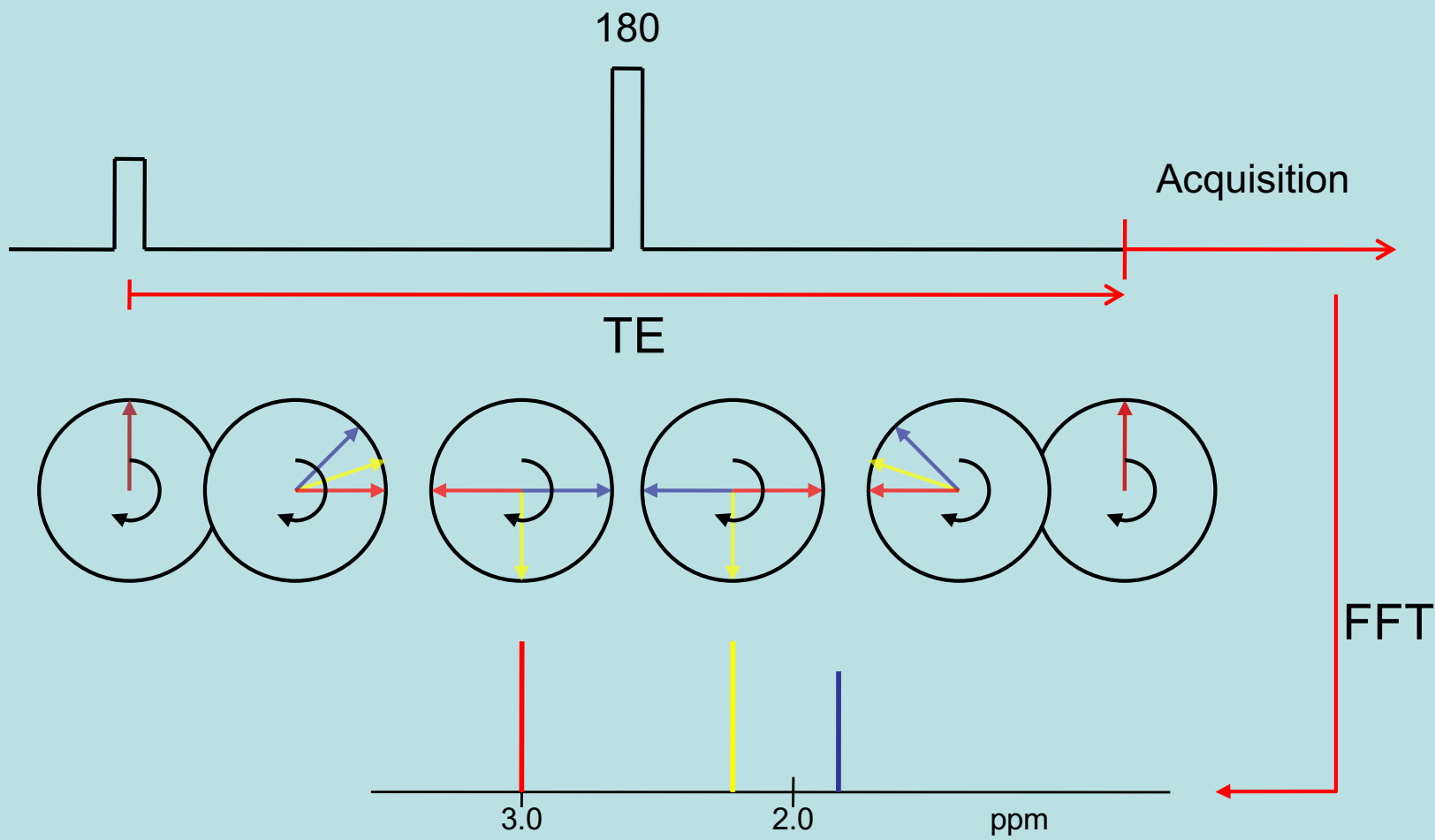
Data of: Magnetic Resonance Spectroscopy Core, Molecular Imaging Branch, NIMH, NIH

LCModel (Version 6.1-0) Copyright: S.W. Provencher. Ref.: Magn. Reson. Med. 30:672-679 (1993).

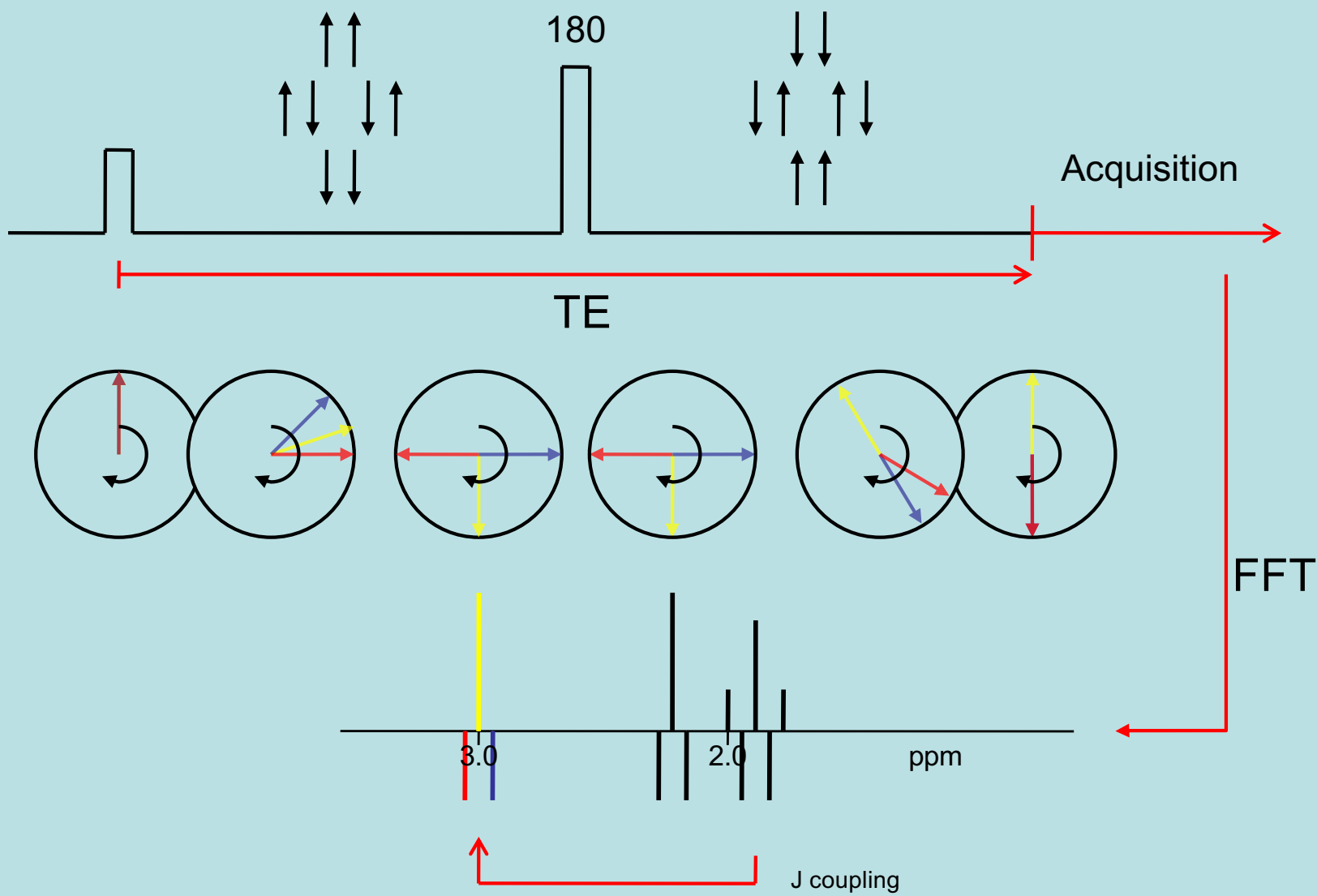
30-August-2004 12:22



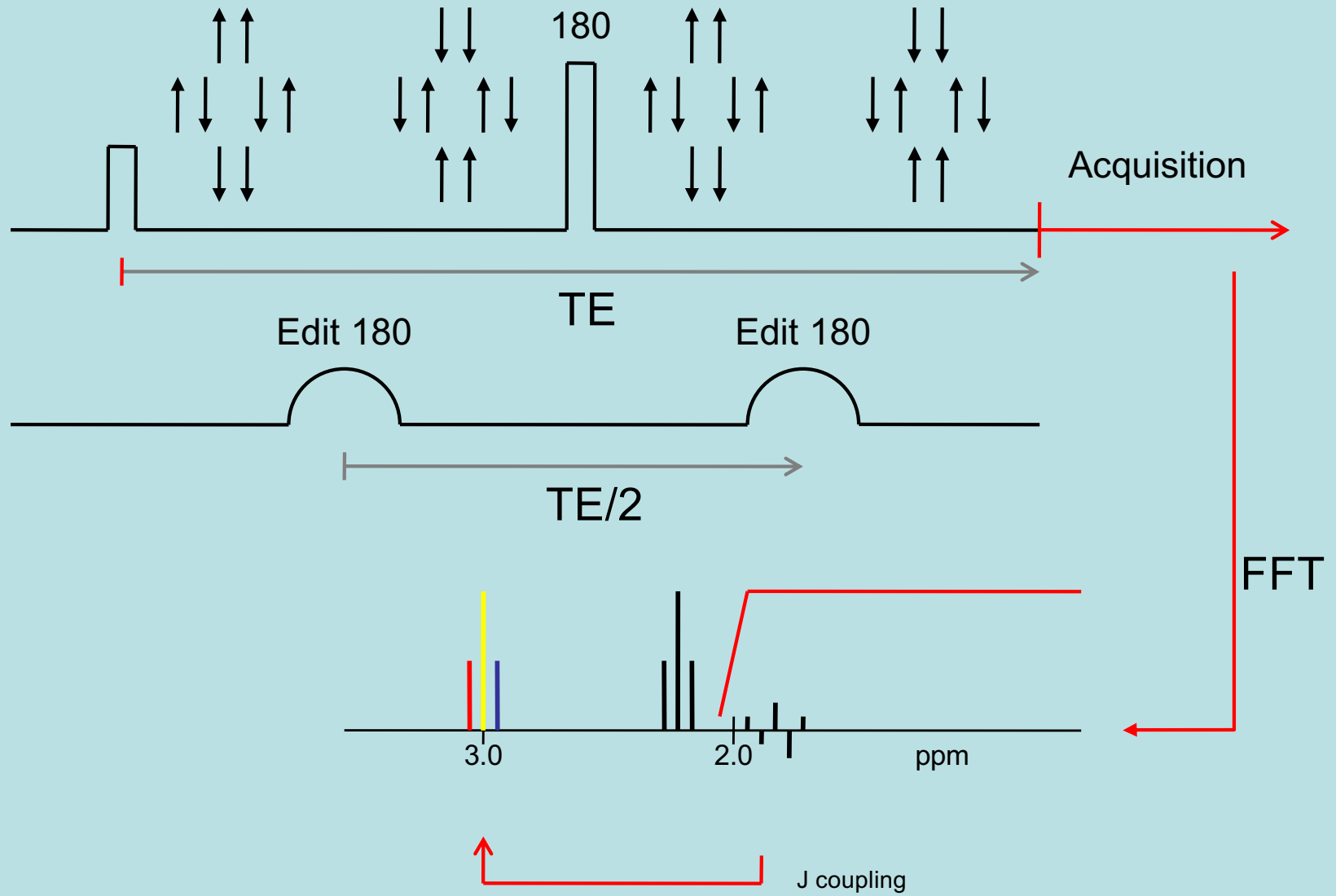
Spin echo

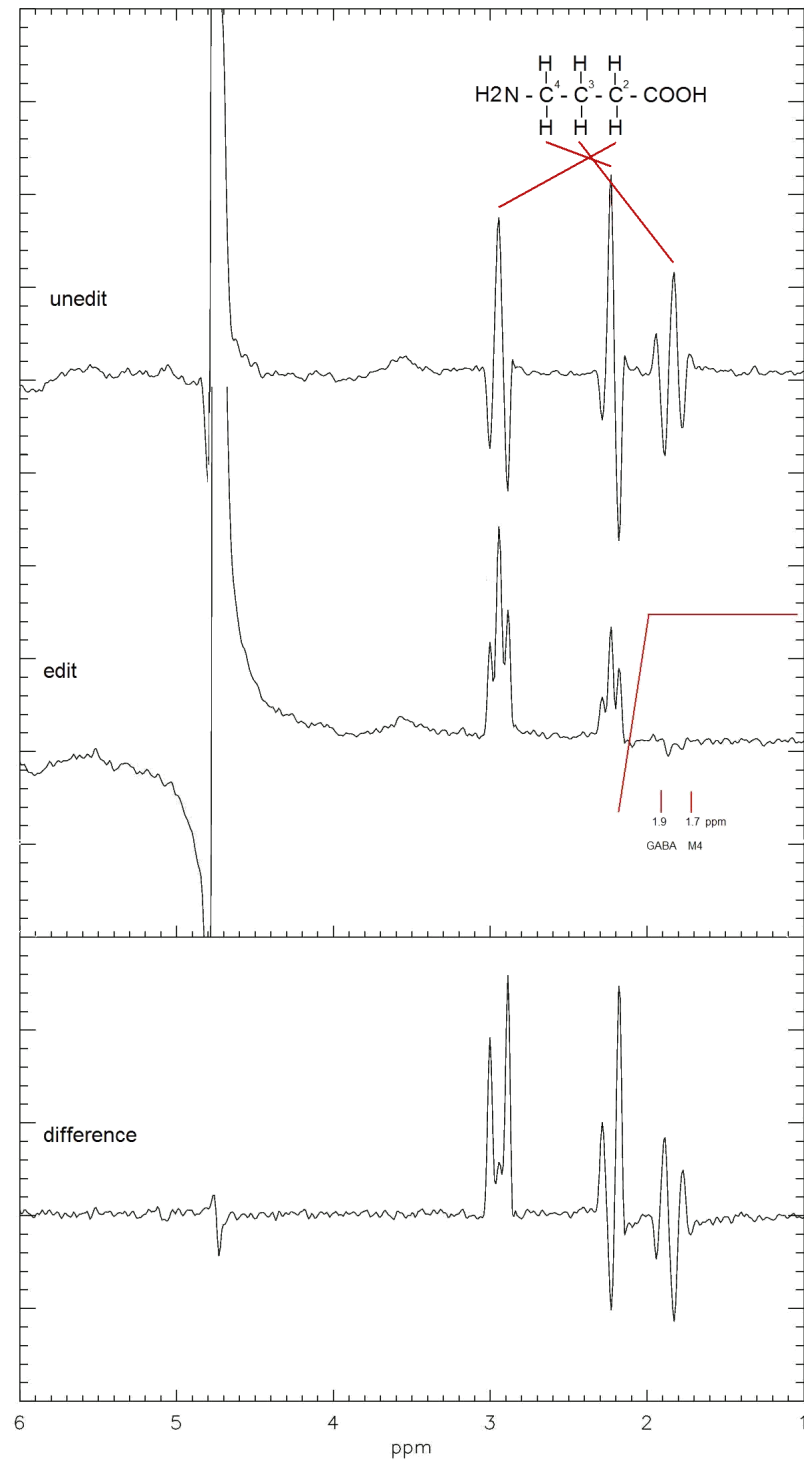


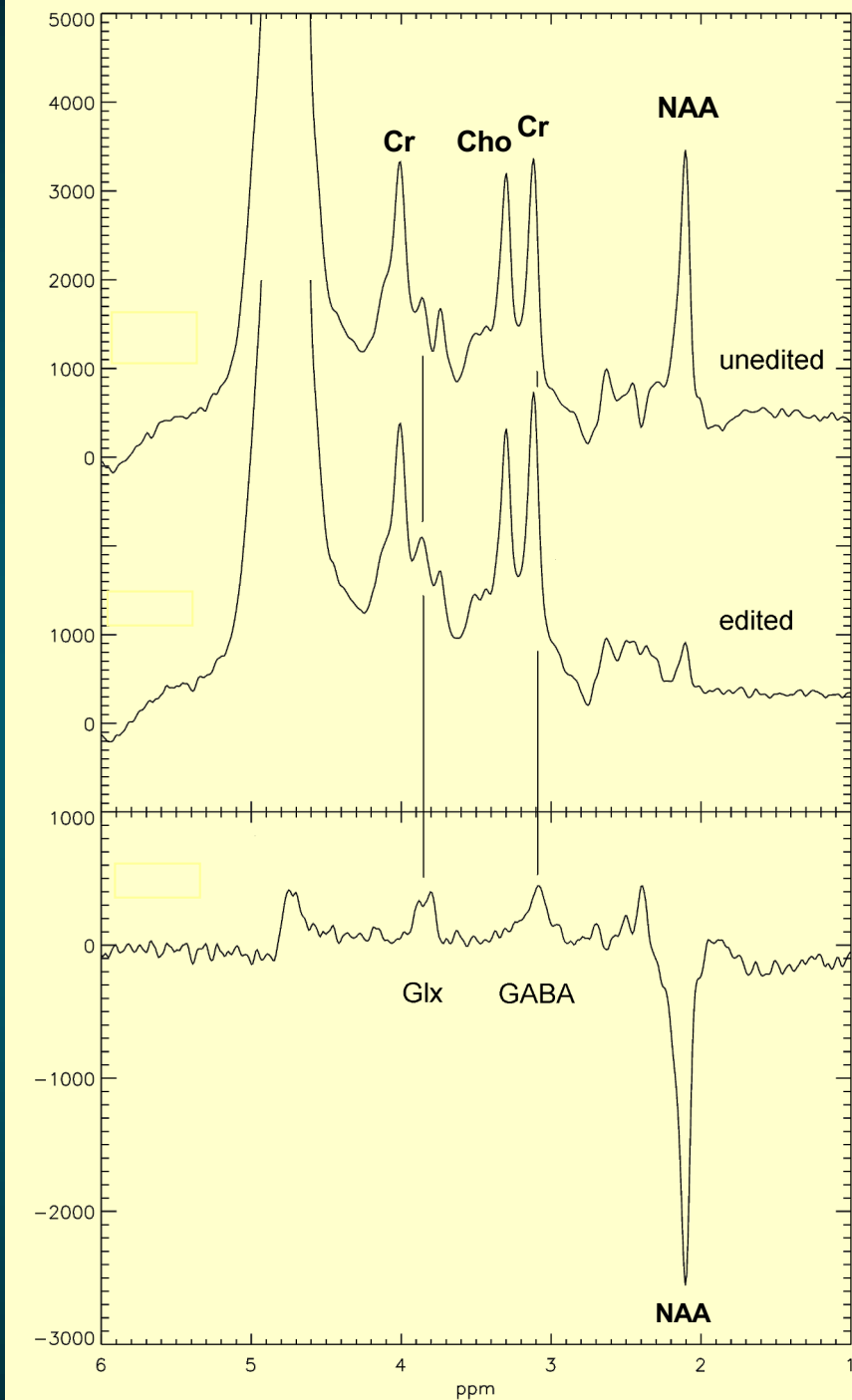
Spin echo and J coupling



Spectral editing







GE 3T scanner
Standard receive/transmit head coil

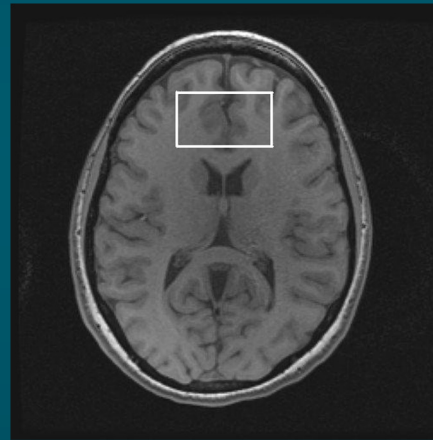
TE = 68ms

TR = 1.5 s

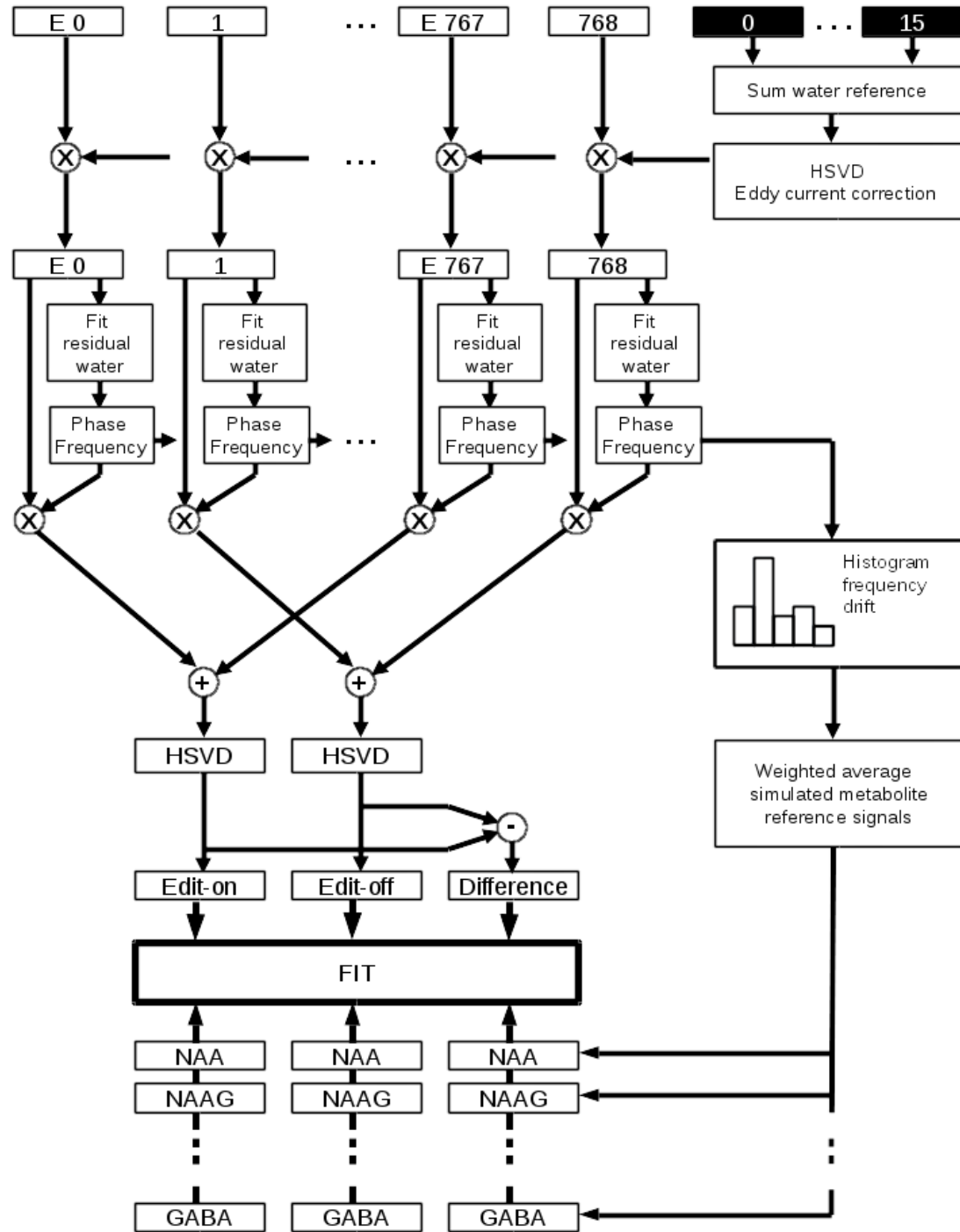
1024 averages

5 or 3 cm l/r, 3 cm a/p, 2cm s/i

scan time **26 min**

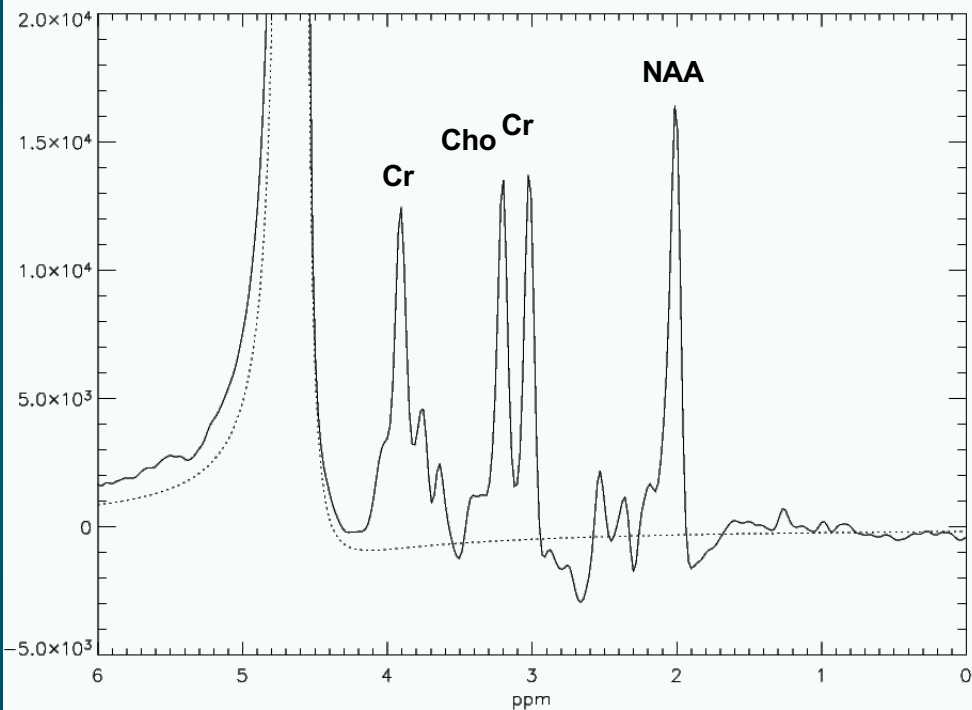


Napapon Sailasuta et al, "Detection of Cerebral GABA in Bipolar Disorder Patients and Healthy Volunteers at 3T", Proc. Intl. Soc. Mag. Reson. Med. 9 (2001) p1011.

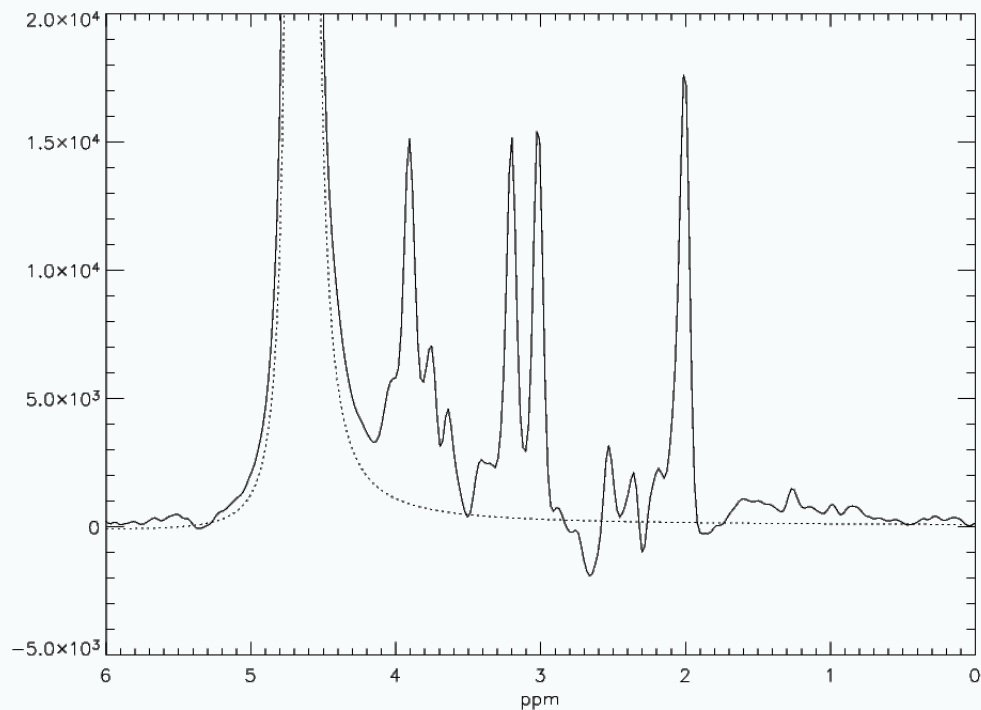


Water reference correction on the non-edited signal

No correction

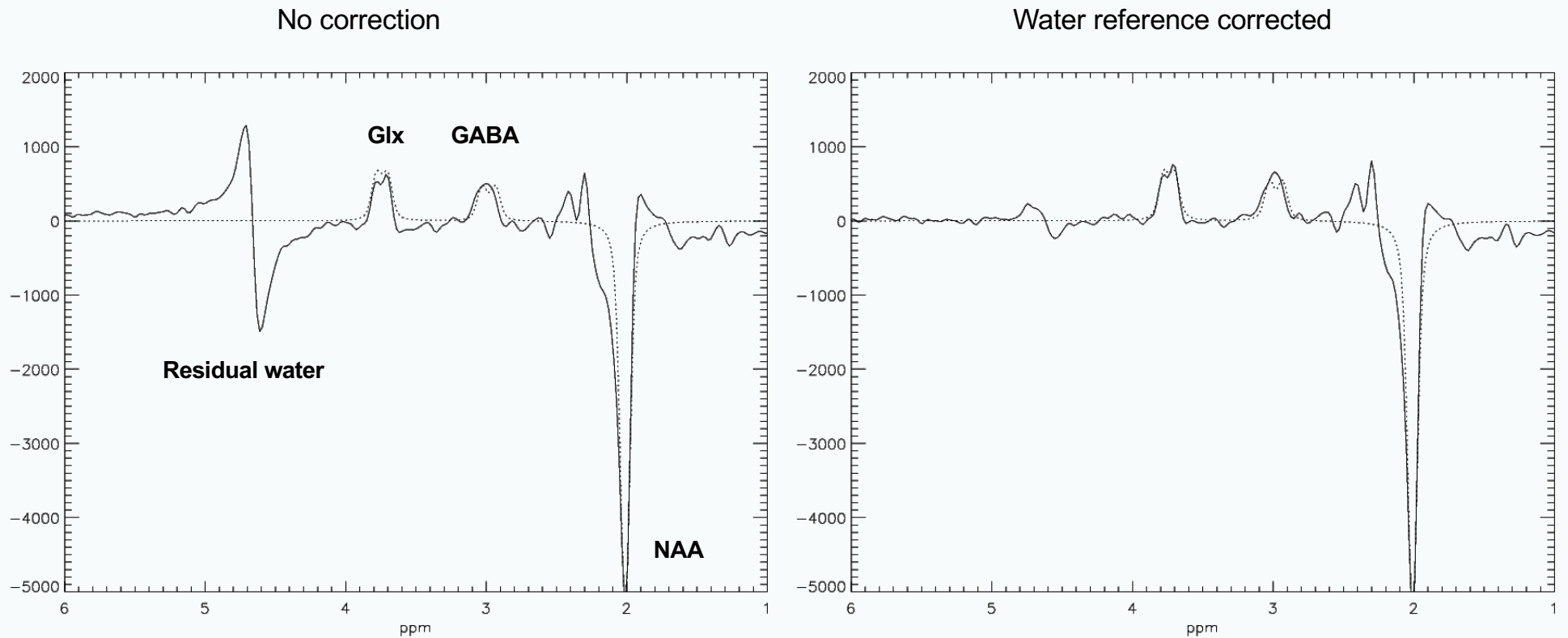


Water reference corrected



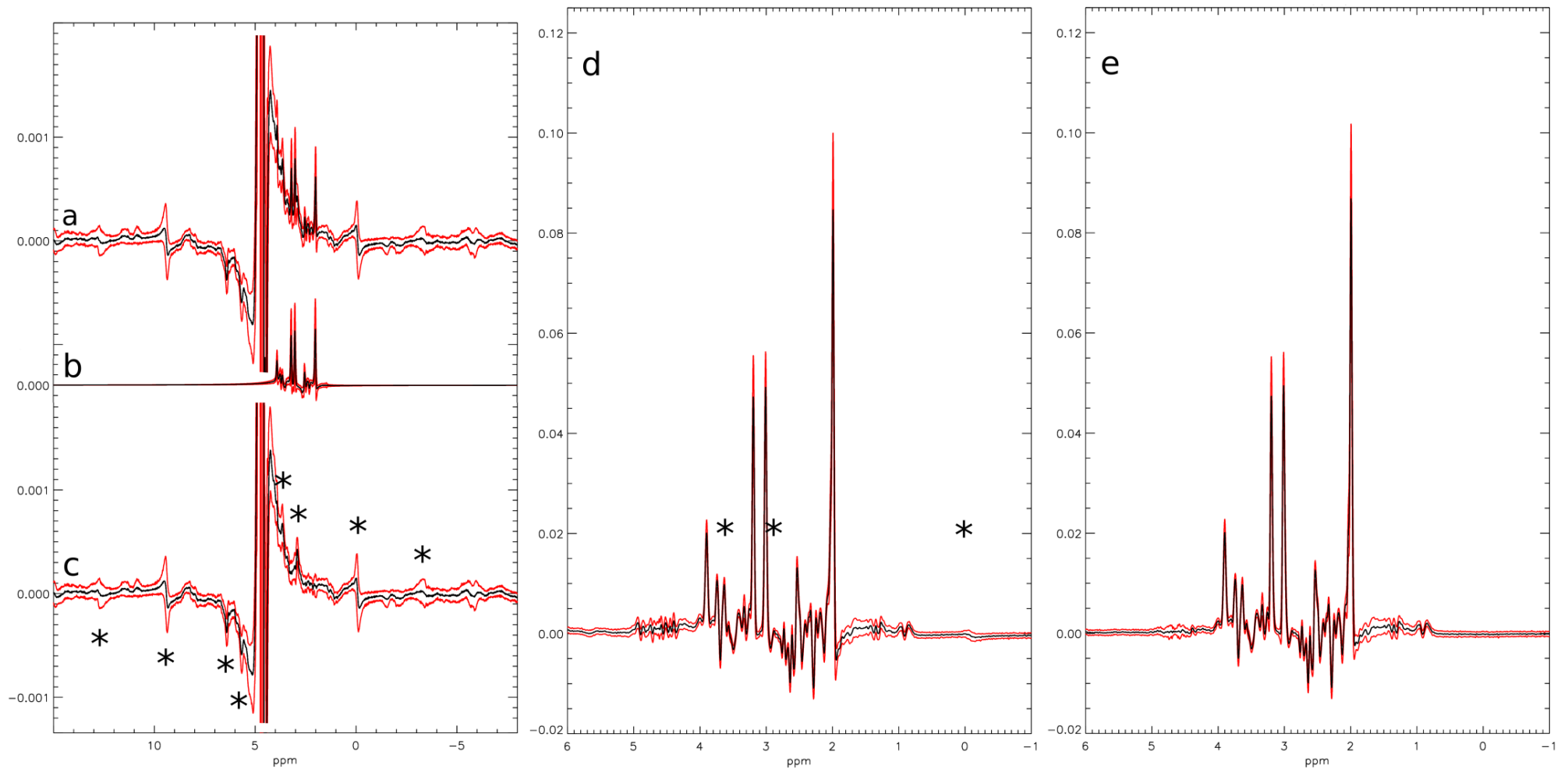
Solid line = data, dotted line = nonlinear gauss/lorentz line fit to residual watersignal

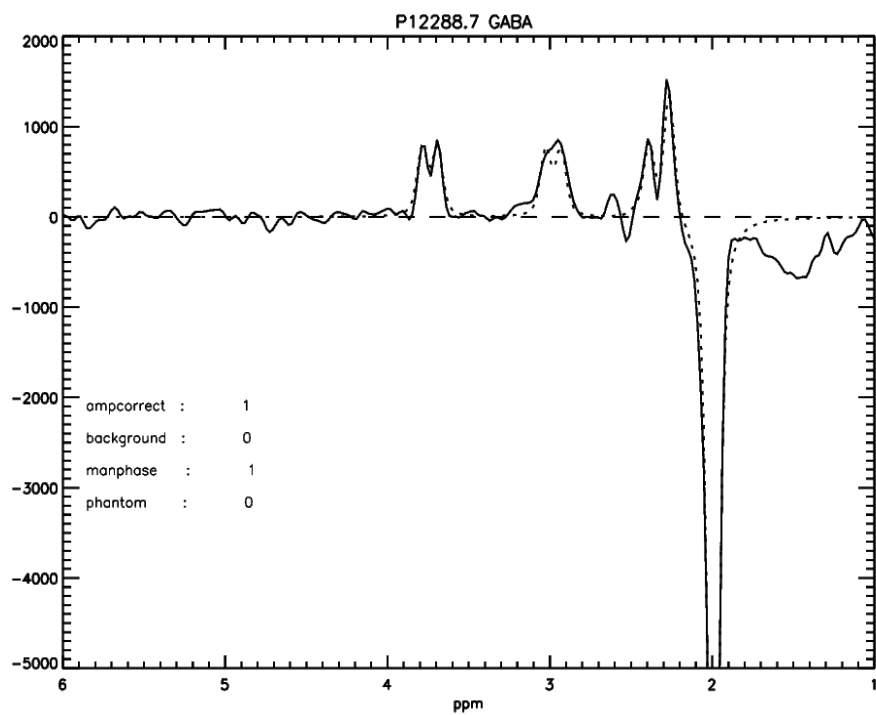
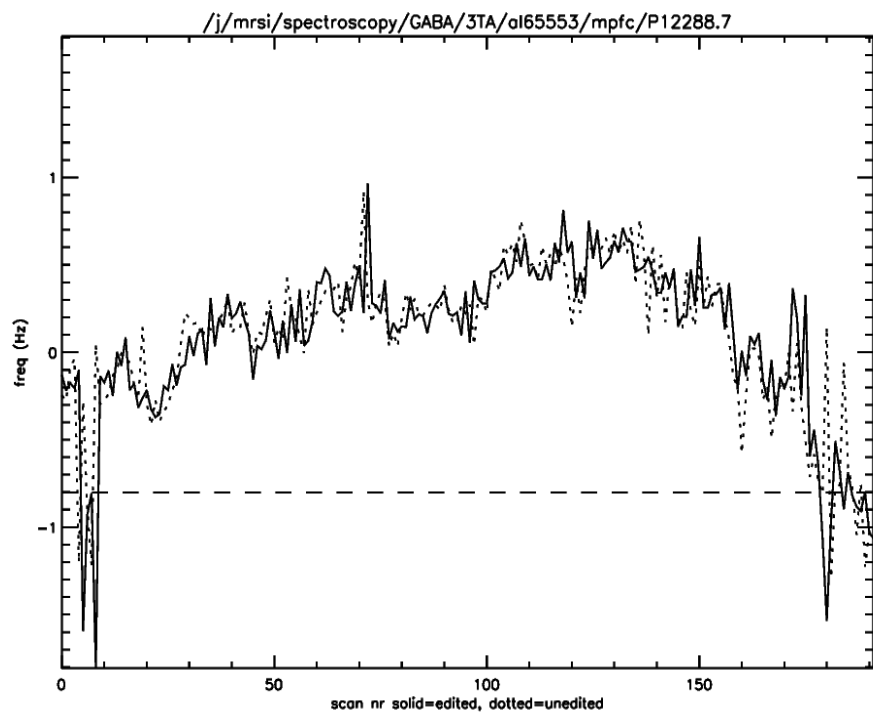
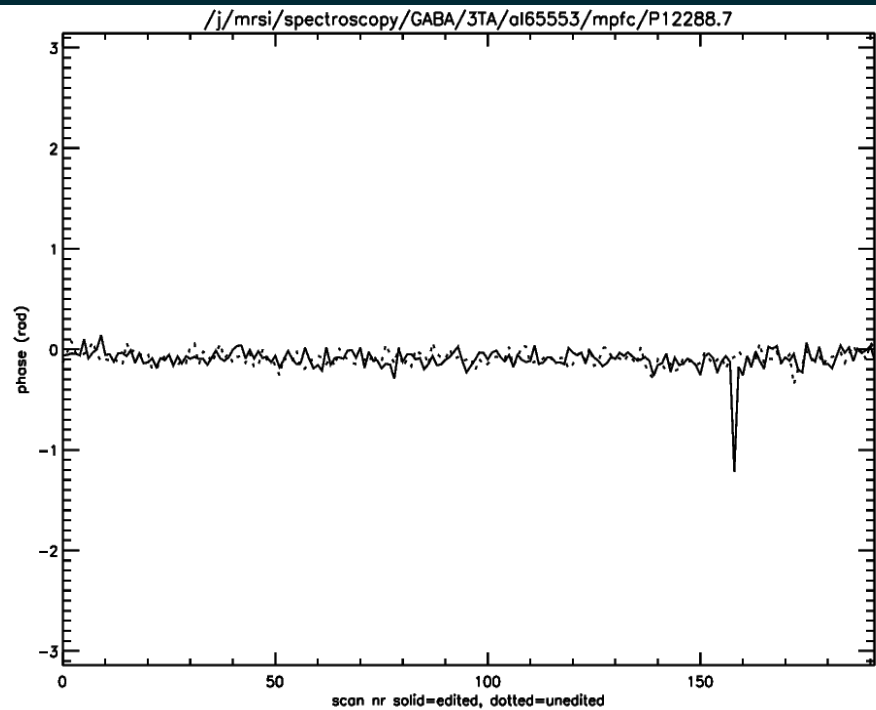
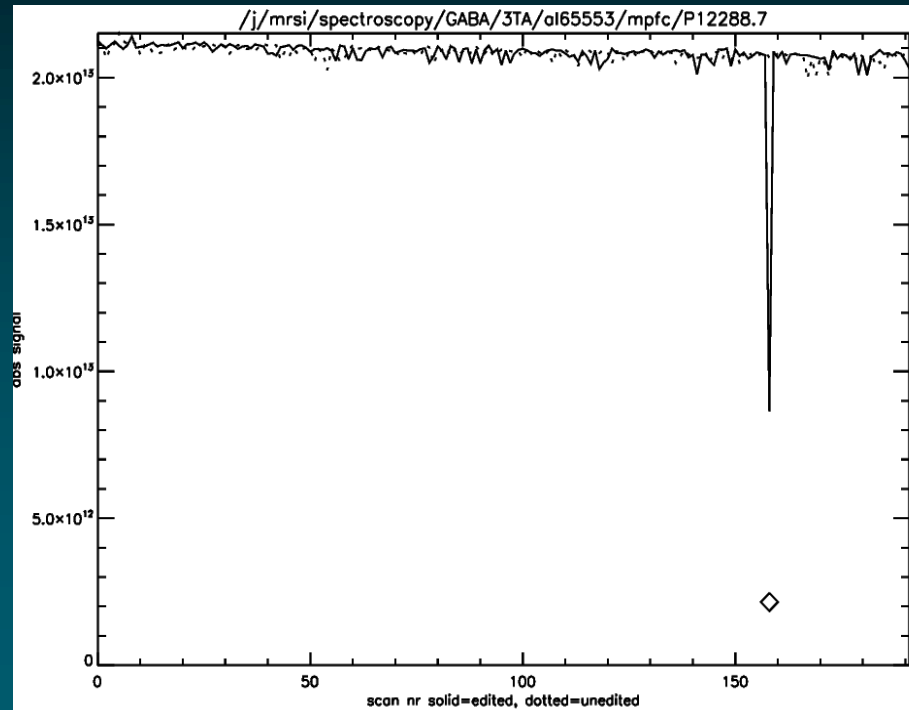
Water reference correction on edited signal



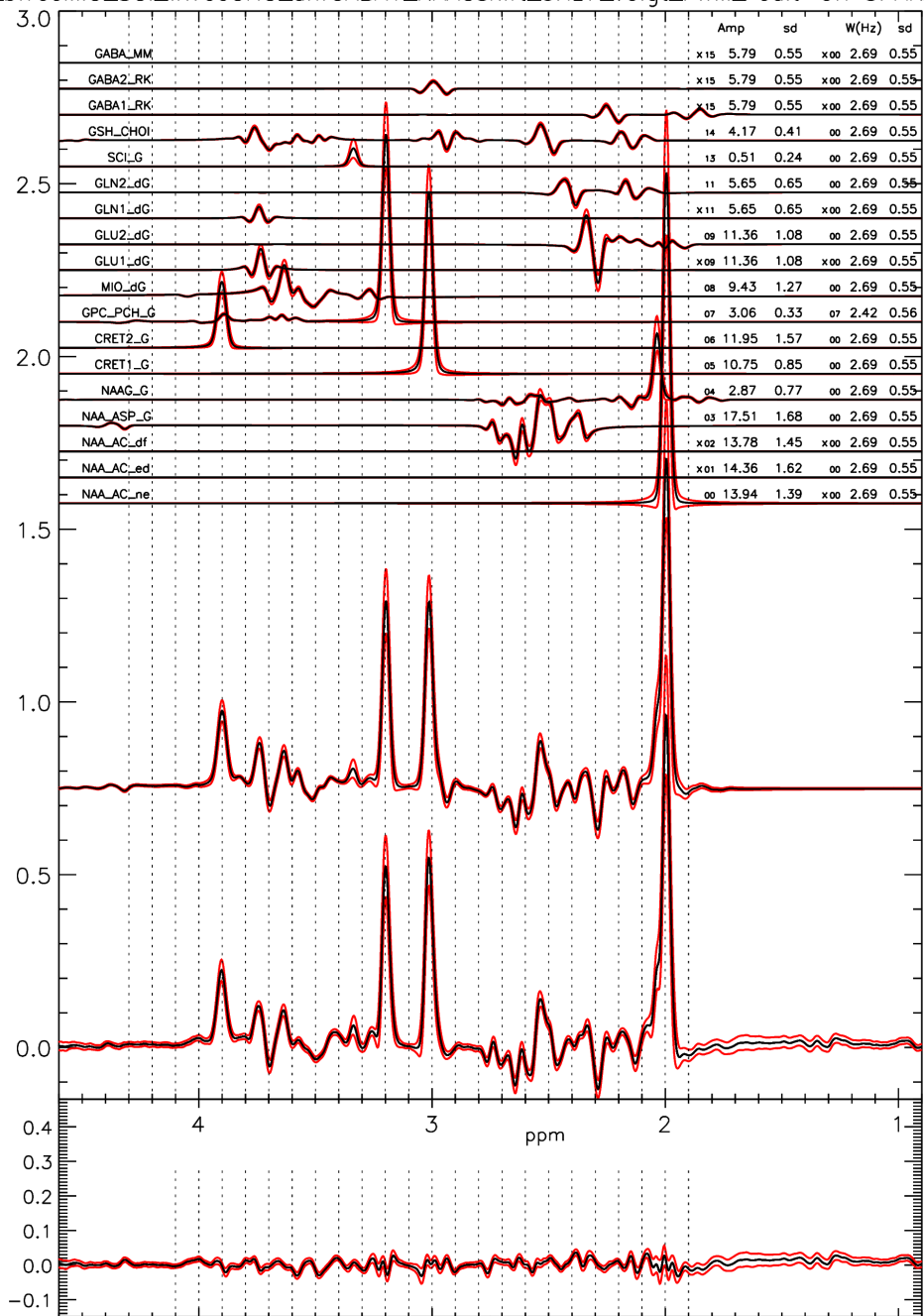
Solid line = data, dotted line = nonlinear gauss/lorentz line fit

Water sideband correction

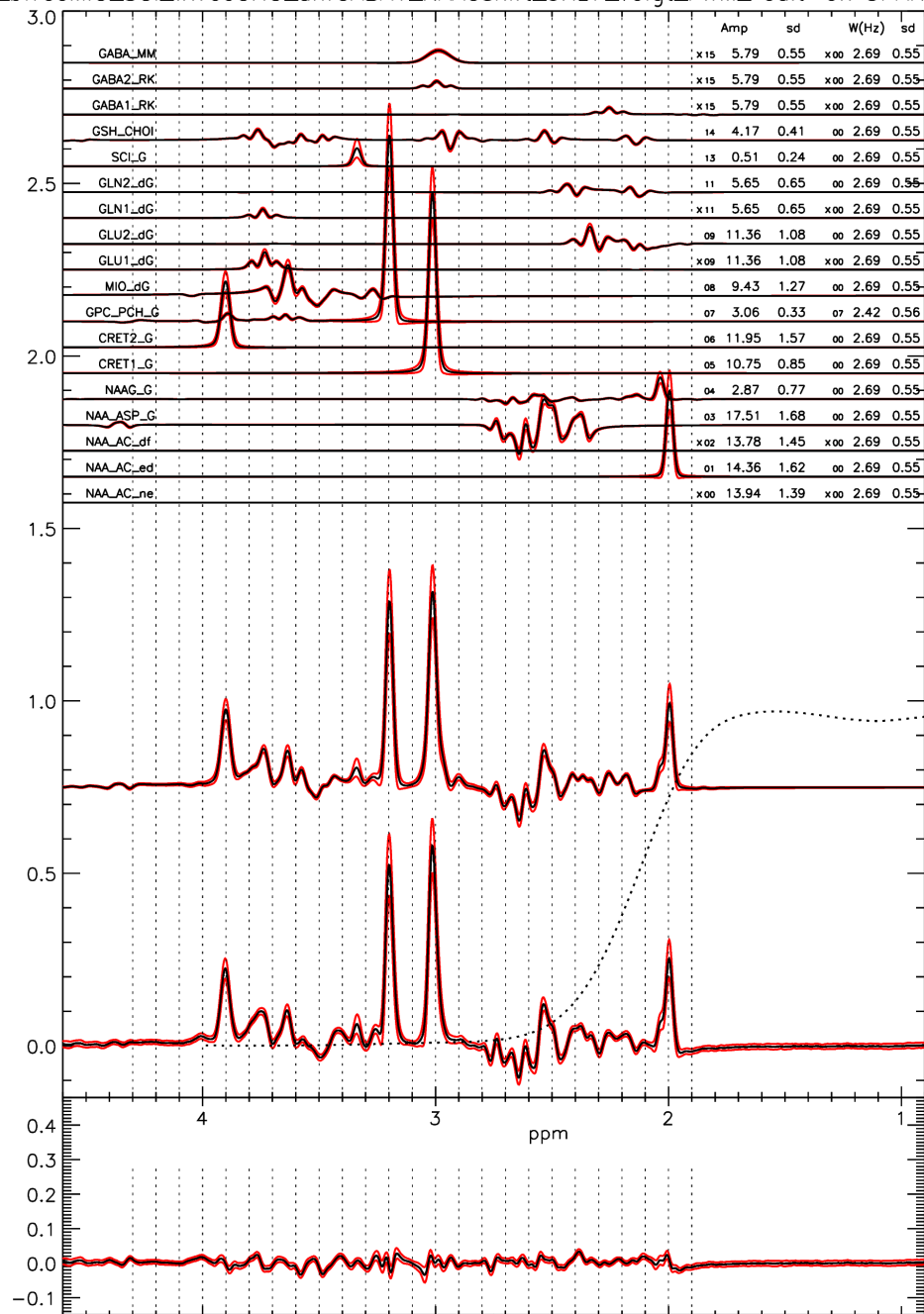




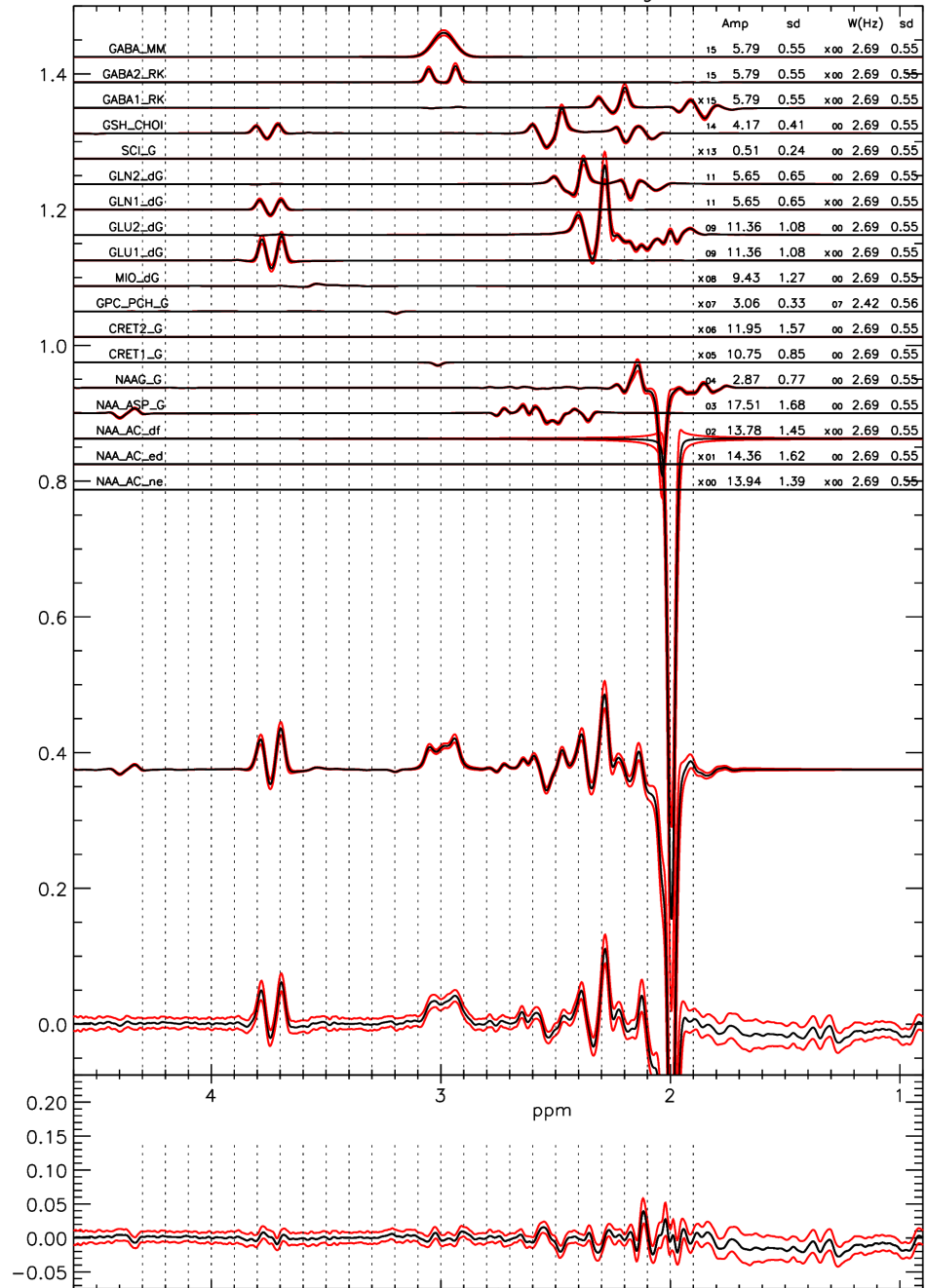
_bfreeMIO_SCI_wfreeCHO_dnfGABA1_NAAGshift_0Hz7_voigt_FWM_ edit-off 3PARALLE



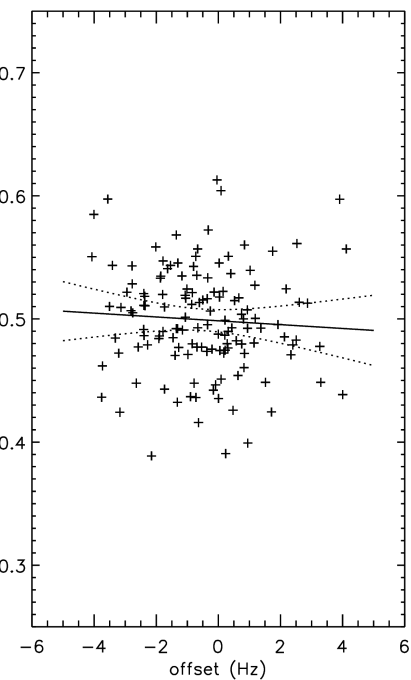
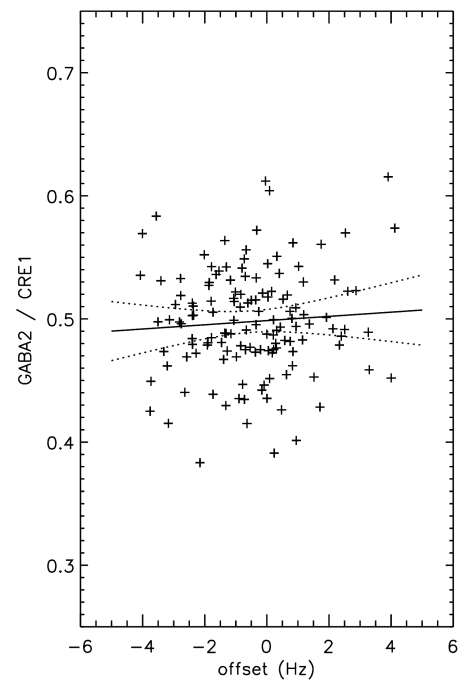
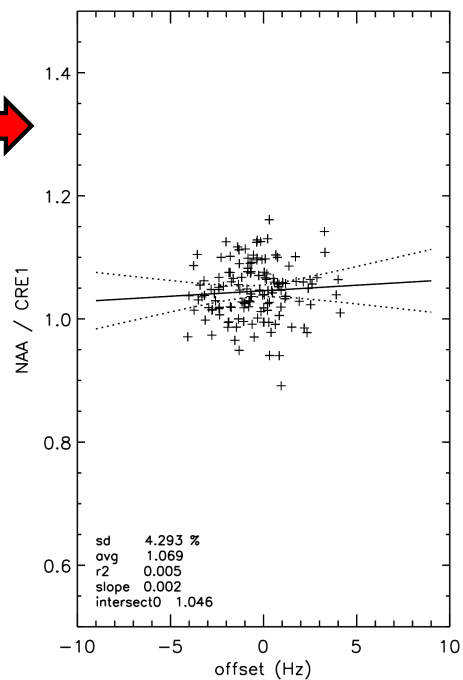
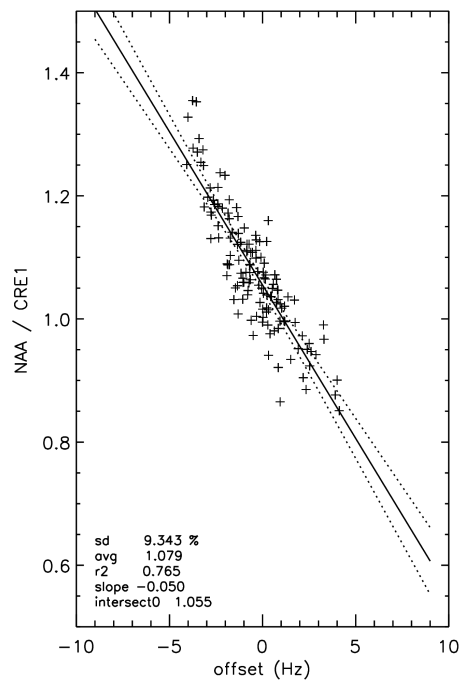
_bfreeMIO_SCI_wfreeCHO_dnfGABA1_NAAGshift_0Hz7_voigt_FWM_ edit-on 3PARALLE

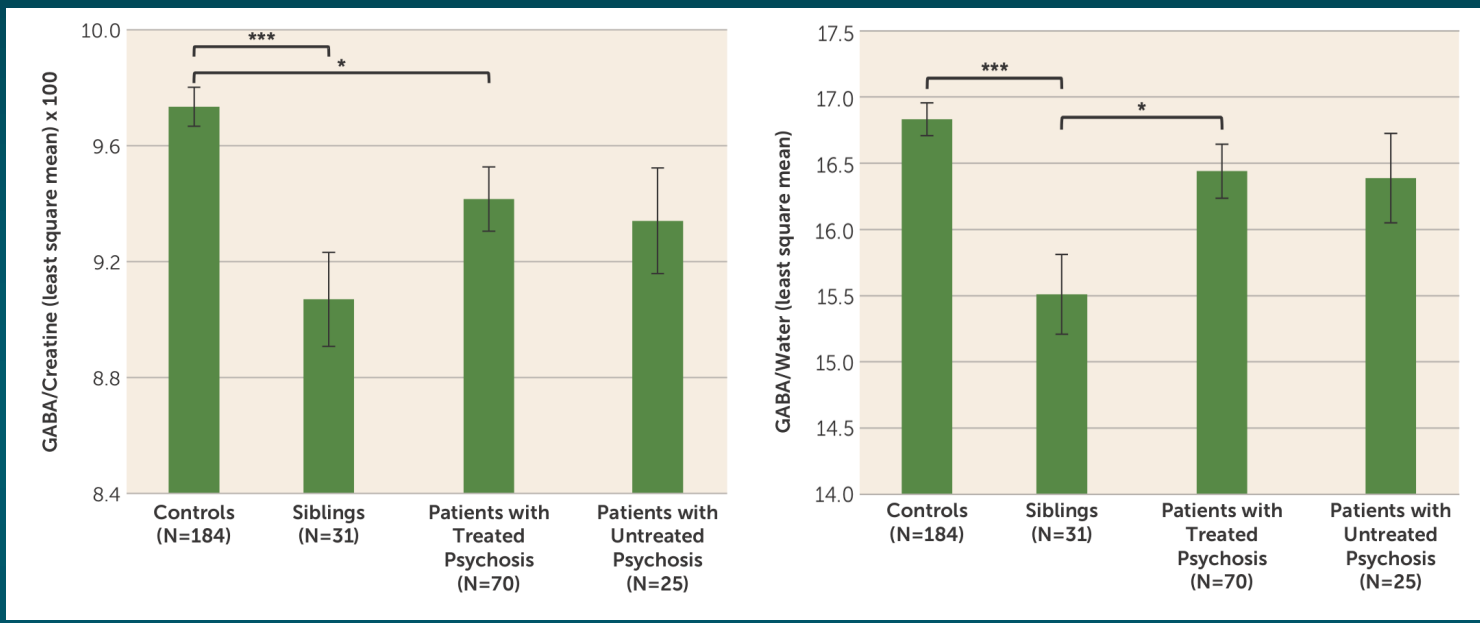


_bfreeMIO_SCI_wfreeCHO_dnfGABA1_NAAGshift_0Hz7_voigt_FWM_difference_3PARALL



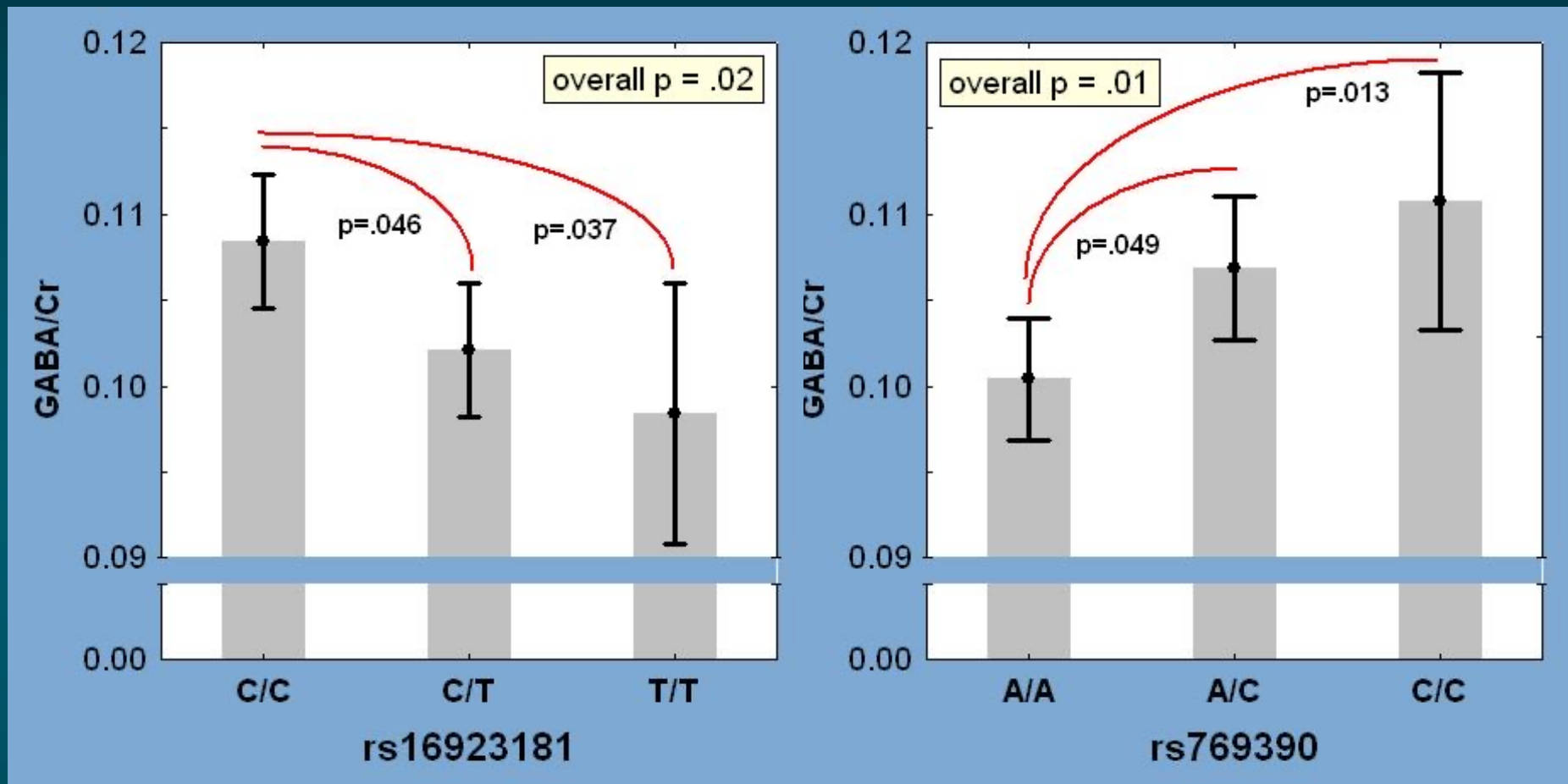
Retrospective drift correction in GABA editing





Prefrontal GABA levels Measured With Magnetic Resonance Spectroscopy in Patients With Psychosis and Unaffected Siblings, Stefano Marenco MD, Christian Meyer Bsc, Susan Kuo BA, Jan Willem van der Veen PhD, Jun Shen PhD, Katherine DeJong BA, Alan S Barnett PhD, Jose A Apud MD PhD, Dwight Dickinson PhD, Daniel R Weinberger MD, Karen F Berman MD. *AJP in Advance* (doi: 10.1176/appi.ajp.2015.15020190)

GAD1 Genotypes Predict GABA/Cr Concentration



GLM models accounted for effects of age and scanner. The “risk” allele is C for both rs16923181 (left) and rs769390 (right). Significant post-hoc comparisons noted in red.

SFN 2008 poster: GAD1 Genotype May Predict GABA Levels in Anterior Cingulate: A Proton Magnetic Resonance Spectroscopy (^1H -MRS) Study. Antonina A. Savostyanova¹, J.W. van der Veen², A. Stern¹, A. S. Barnett¹, J. Shen², B. Kolachana¹, J.H. Callicott¹, R.E. Straub¹, D. R. Weinberger¹, S. Marengo¹

¹Clinical Brain Disorders Branch, NIMH, Bethesda, MD, ²Magnetic Resonance Spectroscopy Unit, NIMH, Bethesda, MD

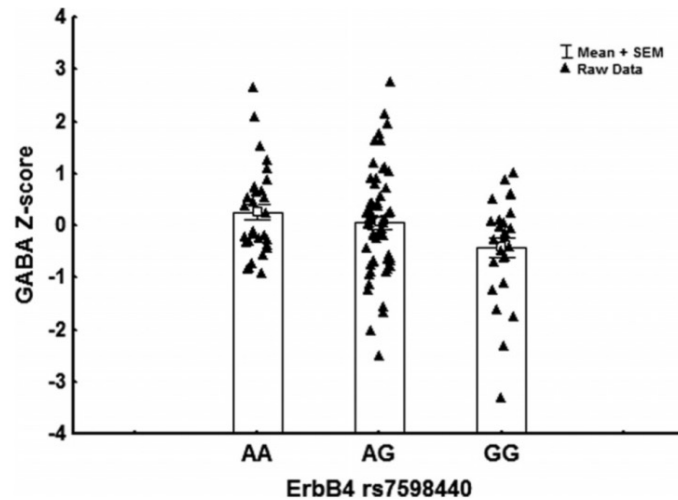


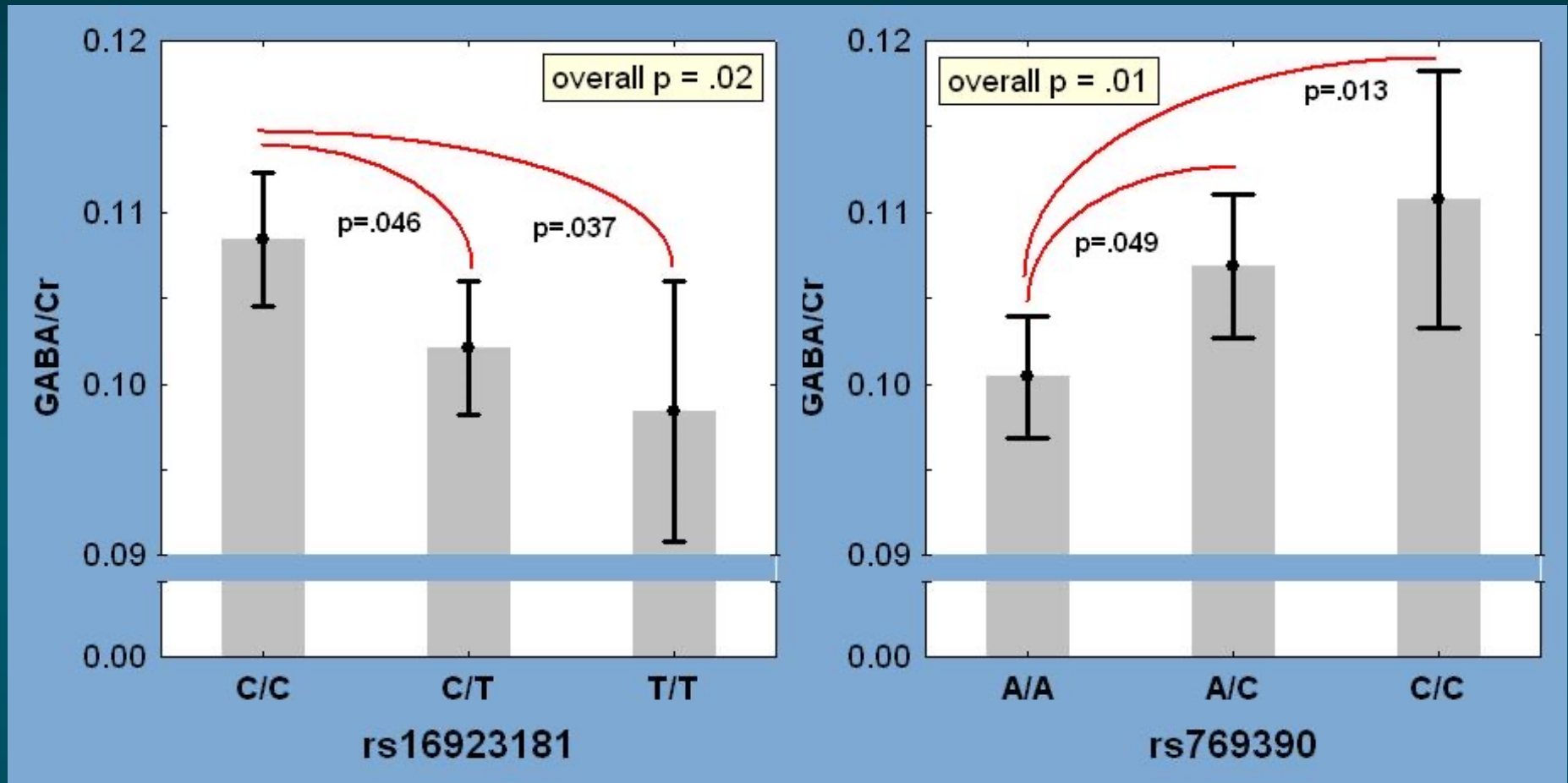
Figure 2. Mean values of GABA for the three genotypes at rs7598440 in ErbB4.

NRG1-ErbB4 signaling controls inhibitory circuit development in the mammalian cortex through ErbB4-dependent regulation of GABAergic interneuron connectivity. Common genetic variation in ErbB4 (rs7598440) has been associated with ErbB4 messenger RNA levels in the human cortex and risk for schizophrenia. Recent work demonstrates that ErbB4 is expressed exclusively on inhibitory interneurons, where its presence on parvalbumin-positive cells mediates the effects of NRG1 on inhibitory circuit formation in the cortex. We therefore hypothesized that genetic variation in ErbB4 at rs7598440 would impact indices of GABA concentration in the human cortex. We tested this hypothesis in 116 healthy volunteers by measuring GABA and GLX (glutamate + glutamine) with proton magnetic resonance spectroscopy in the dorsal anterior cingulate gyrus. ErbB4 rs7598440 genotype significantly predicted cortical GABA concentration ($p = 0.014$), but not GLX ($p = 0.51$), with A allele carriers having higher GABA as predicted by the allelic impact on ErbB4 expression. These data establish an association of ErbB4 and GABA in human brain and have implications for understanding the pathogenesis of schizophrenia and other psychiatric disorders.

Genetic Association of ErbB4 and Human Cortical GABA Levels In Vivo,

Stefano Marengo, Matthew Geramita, Jan Willem van der Veen, Alan S Barnett, Bhaskar Kolachana, Jun Shen, Daniel R Weinberger, Amanda J Law. J Neurosci 2011 31 (32) 11628-11632

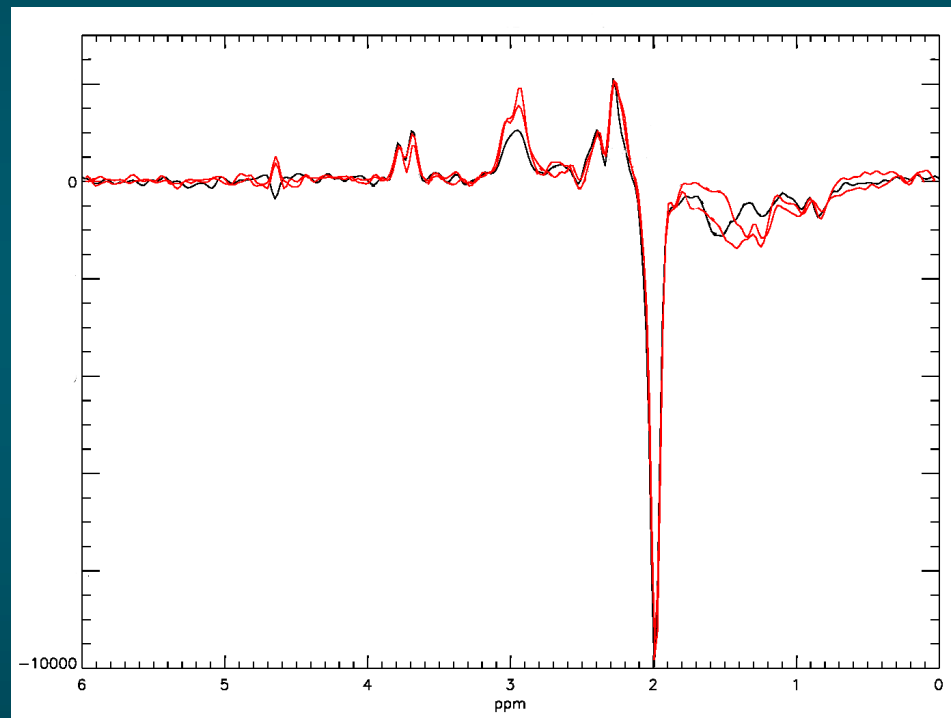
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SSADH GABA spectrum



William Theodore (ninds).

Magnetic resonance spectroscopy core

Jun Shen

Li An

Clinical Brain Disorder Branch, GCAP

Stefano Marengo

NINDS, Clinical epilepsy section

William Theodore

NINDS, Human motor control section

Mark Hallett

Silvina Horowitz