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NEUROIMAGING

7T MRS Glutamate and GABA in Alzheimer's Disease

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Abstract

Background: Functional neuroimaging studies suggest a dynamic trajectory in Alzheimer's disease (AD), with early hyperconnectivity followed by hypoconnectivity due to pathologic progression. This study aimed to investigate this hypothesis using neurochemical markers derived from high-field magnetic resonance spectroscopy (MRS).

Method: We analyzed data from 126 older adults enrolled in the NeuroMET studies, spanning from normal aging to dementia due to suspected AD. Using ultra-high-field 7 Tesla MRS, we quantified levels of the neurotransmitters glutamate (excitatory) and GABA (inhibitory) in the precentral cortex. Plasma *p* -Tau181 was used as a proxy for AD pathology, and memory was assessed using the NeuroMET Memory Metric (NMM). A *p* -Tau181 threshold of >2.08 pg/mL was applied as an estimated marker of amyloid positivity (Aß+). Linear mixed-effects models, adjusted for age at baseline, were used to evaluate associations and interaction effects.

Result: Glutamate levels showed a non-linear association with age, decreasing up to around 70 years and increasing thereafter, while GABA levels remained stable (Figure 1A–C). Before reaching the suggested pathological conversion threshold for amyloid positivity, both glutamate and GABA showed a slight, non-significant increase in individuals with higher *p* -Tau181 levels (Figure 1D–F). Notably, amyloid status moderated the relationship between memory ability and glutamate levels (Figure 1G–I). Among Aß-negative individuals, lower memory ability was associated with elevated glutamate, potentially reflecting a very early compensatory response.

Conclusion: Our findings support the hypothesis of a non-linear neurochemical trajectory in aging and early AD pathology. The observed age-dependent fluctuations in glutamate, together with subtle shifts in response to rising plasma *p* -Tau181, may reflect early pathologic or compensatory mechanisms. The interaction between

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glutamate and memory ability, particularly in supposedly Aß-negative individuals, suggests that excitatory neurotransmission could transiently support cognitive function in the face of emerging pathology. Notably, the threshold of plasma *p*-Tau181 used to define amyloid positivity may identify individuals in progressed stages, potentially missing earlier windows of therapeutic opportunity. As potential treatments may have markedly different effects depending on the stage of disease progression, investigating the trajectory of neuronal connectivity and activity is critical.

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Table 1. Linear mixed-effects models assessing associations between plasma p-Tau181 levels and glutamate, GABA, and the glutamate/GABA ratio across time, while adjusting for age (at baseline) and accounting for random intercepts per subject. Significant associations ($p < 0.05$) are bolded.

Model Glutamate lmer(glu ~ ns(pTau, df = 3) * ns(year, df = 3) + ns(age_bl, df = 2) + (1 | record_id)			**Model GABA** lmer(gaba ~ ns(pTau, df = 3) * ns(year, df = 4) + ns(age_bl, df = 1) + (1 | record_id)			**Model Glutamate/GABA** lmer(glu_gaba ~ ns(pTau, df = 3) * ns(year, df = 3) + ns(age_bl, df = 2) + (1 | record_id)		
age_bl	ß [95% CI]	p	**age_bl**	ß [95% CI]	p	**age_bl**	ß [95% CI]	p
60	**-0,12 [-0,20; -0,03]**	**0,006**	60	-0,01 [-0,03; 0,01]	0,201	60	-0,02 [-0,06; 0,01]	0,192
65	**-0,08 [-0,14; -0,02]**	**0,012**				65	-0,01 [-0,04; 0,01]	0,331
70	-0,01 [-0,05; 0,02]	0,435				70	0,01 [-0,01; 0,02]	0,510
75	**0,06 [0,00; 0,11]**	**0,046**				**75**	**0,03 [0,00; 0,05]**	**0,042**
80	**0,10 [0,02; 0,18]**	**0,016**				**80**	**0,04 [0,00; 0,07]**	**0,037**
p-Tau181	ß [95% CI]	p	**p-Tau181**	ß [95% CI]	p	**p-Tau181**	ß [95% CI]	p
1,25	0,42 [-0,90; 1,74]	0,535	1,25	0,54 [-0,02; 1,11]	0,059	1,25	-0,41 [-1,01; 0,19]	0,183
1,88	-0,10 [-0,50; 0,30]	0,612	1,88	0,12 [-0,05; 0,30]	0,156	1,88	-0,16 [-0,34; 0,02]	0,082
2,5	-0,35 [-0,86; 0,15]	0,166	2,5	-0,10 [-0,32; 0,12]	0,359	2,5	-0,02 [-0,25; 0,21]	0,877
5	-0,06 [-0,28; 0,15]	0,560	5	-0,01 [-0,11; 0,08]	0,786	5	-0,01 [-0,11; 0,09]	0,864

Model Glutamate lmer(glu ~ pTau_group * ns(nmm, df = 4) + ns(year, df = 3) + ns(age_bl, df = 2) + (1 | record_id)			**Model GABA** lmer(gaba ~ pTau_group * ns(nmm, df = 3) + ns(year, df = 3) + ns(age_bl, df = 2) + (1 | record_id)			**Model Glutamate/GABA** lmer(glu_gaba ~ pTau_group * ns(nmm, df = 3) + ns(year, df = 3) + ns(age_bl, df = 2) + (1 | record_id)		
	Aß-			**Aß-**			**Aß-**	
NMM	ß [95% CI]	p	**NMM**	ß [95% CI]	p	**NMM**	ß [95% CI]	p
-2.0	**1,52 [0,17; 2,88]**	**0,028**	-2.0	0,10 [-0,45; 0,64]	0,728	-2.0	0,03 [-0,53; 0,59]	0,915
-1.0	-0,39 [-1,05; 0,26]	0,239	-1.0	0,01 [-0,28; 0,31]	0,921	-1.0	-0,02 [-0,32; 0,27]	0,876
-0.5	**-1,57 [-2,52; -0,62]**	**0,001**	-0.5	-0,04 [-0,26; 0,19]	0,758	-0.5	-0,06 [-0,29; 0,17]	0,630
0.5	0,15 [-0,73; 1,02]	0,745	0.5	-0,10 [-0,40; 0,19]	0,491	0.5	-0,09 [-0,40; 0,22]	0,580
1.0	0,49 [-0,29; 1,27]	0,214	1.0	-0,07 [-0,26; 0,12]	0,454	1.0	-0,04 [-0,25; 0,17]	0,708
2.0	-0,56 [-1,59; 0,46]	0,278	2.0	-0,03 [-0,40; 0,35]	0,891	2.0	0,03 [-0,40; 0,46]	0,886
	Aß+			**Aß+**			**Aß+**	
NMM	ß [95% CI]	p	**NMM**	ß [95% CI]	p	**NMM**	ß [95% CI]	p
-2.0	0,31 [-0,08; 0,7]	0,122	-2.0	0,17 [-0,02; 0,35]	0,075	-2.0	-0,09 [-0,28; 0,11]	0,379
-1.0	0,07 [-0,29; 0,44]	0,689	-1.0	0,10 [-0,03; 0,23]	0,143	-1.0	-0,06 [-0,20; 0,07]	0,342
-0.5	-0,07 [-0,63; 0,49]	0,814	-0.5	0,05 [-0,12; 0,23]	0,549	-0.5	-0,05 [-0,23; 0,13]	0,584
0.5	0,25 [-0,94; 1,45]	0,675	0.5	0,01 [-0,20; 0,22]	0,914	0.5	-0,04 [-0,26; 0,17]	0,693
1.0	0,00 [-0,90; 0,90]	0,998	1.0	0,07 [-0,31; 0,45]	0,715	1.0	-0,07 [-0,49; 0,34]	0,731
2.0	-0,80 [-3,85; 2,25]	0,606	2.0	0,16 [-0,72; 1,03]	0,723	2.0	-0,12 [-1,08; 0,84]	0,811

Abbreviations: Aß = Amyloid-beta; CI = Confidence Interval; GABA = Gamma-Aminobutyric Acid; Glu = Glutamate; nmm = NeuroMET Memory Metric; p-Tau = Phosphorylated Tau.

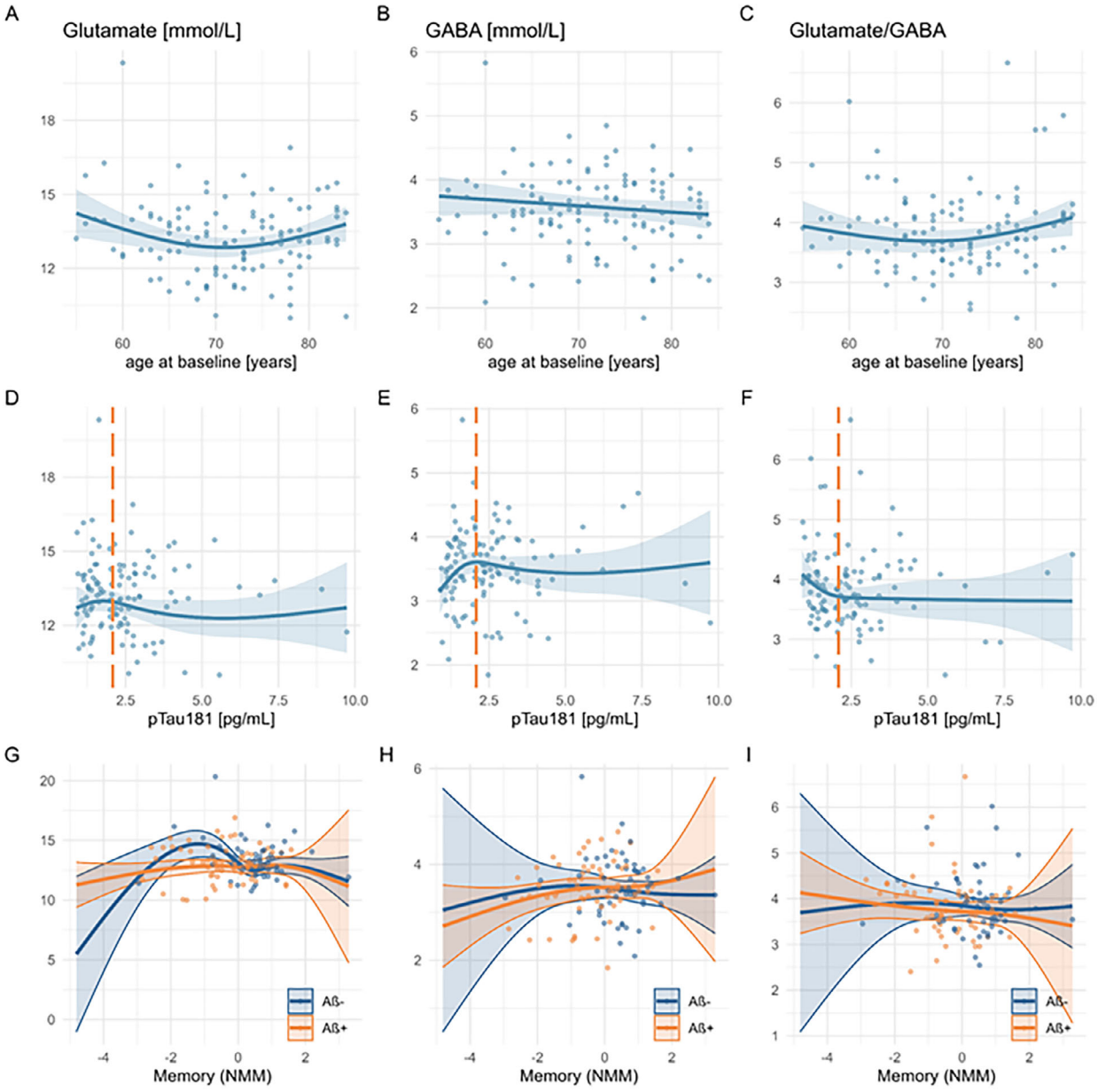

Figure 1: Association between neurotransmitter levels and age, plasma pTau181 and memory ability indicated by the NMM. (A–C) Metabolite levels across age for glutamate (A), GABA (B), and glutamate/GABA ratio (C), based on linear mixed-effects models controlling for pTau181, and weighted by metabolite-specific measures of uncertainties (CRLBs). **(D–F)** Predicted metabolite levels across plasma pTau181 concentrations for glutamate (D), GABA (E), and glutamate/GABA ratio (F), adjusted for age at baseline and weighted by metabolite-specific CRLBs. Dashed vertical lines indicate the previously established cut-off of 2.08 pg/mL for elevated pTau181. **(G–I)** Predicted metabolite levels across memory ability (NMM scores) stratified by Aβ status (estimated by plasma pTau181), again adjusted for age at baseline and weighted by metabolite-specific CRLBs. Shaded areas represent 95% confidence intervals; data points reflect individual measurements. *Abbreviations: Aβ = amyloid-beta; CRLB = Cramér–Rao lower bound; GABA = γ-aminobutyric acid; NMM = NeuroMET Memory Metric.*