

Supplementary information for:

Hippocampal subfield plasticity is associated with improved spatial memory

Authors:

Henning Boecker^{1,2}, Marcel Daamen², Lukas Kunz³, Melanie Geiß¹, Moritz Müller¹, Thomas Neuss¹, Leonie Henschel², Rüdiger Stirnberg², Neeraj Upadhyay^{1,2}, Lukas Scheef¹, Jason A. Martin¹, Tony Stöcker², Alexander Radbruch⁴, Ulrike Attenberger⁵, Nikolai Axmacher⁶, Angelika Maurer^{1,2}

Affiliations:

¹ Clinical Functional Imaging Lab, Department of Diagnostic and Interventional Radiology, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany

² German Center for Neurodegenerative Diseases, Venusberg-Campus 1/99, 53127 Bonn, Germany

³ Department of Epileptology, University of Bonn Medical Centre, Bonn, Germany

⁴ Department of Neuroradiology, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany

⁵ Department of Diagnostic and Interventional Radiology, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany

⁶ Department of Neuropsychology, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

Corresponding Author

Prof. Henning Boecker

Group Leader of Clinical Functional Imaging Lab

Department of Diagnostic and Interventional Radiology

University Hospital Bonn

Venusberg-Campus 1, Building 07

D-53127 Bonn

Phone: +49 228 – 287 15980

Email: henning.boecker@ukbonn.de

ORCID: <https://orcid.org/0000-0003-2346-0598>

Supplementary Table 1: Background characteristics for included cases vs. drop-outs

Variable	Included N=27 (17 INT/10 CON)	Dropouts N=15 (10 INT/5 CON)	Statistics
Sex (m/f)	12/15	8/7	$\chi^2(1, N= 42) = 0.05, p = 0.827$
Age [years]	23.9 ± 4.0	24.5 ± 4.1	$t(40)=-0.49, p=0.626, d=-0.16$
Height [cm]	174.8 ± 10.8	174.0 ± 8.5	$t(40)=0.25, p=0.804, d=0.08$
Weight [kg]	70.4 ± 14.5	75.3 ± 17.9	$t(40)=-0.95, p=0.346, d=-0.31$
BMI [$\text{kg} \cdot \text{m}^{-2}$]	22.9 ± 3.6	24.9 ± 5.7	$t(40)=-1.33, p=0.191, d=-0.44$
HR _{max} [bpm]	199 ± 8	197 ± 9	$t(39)=0.92, p=0.361, d=0.31$
WST IQ	107 ± 9	104 ± 8	$t(38)=0.97, p=0.338, d=0.34$

Abbreviations: BMI = body mass index; CON = control group; HR_{max} = maximum heart rate in performance diagnostic; INT = intervention group; WST IQ = verbal intelligence quotient derived from German vocabulary test.

Supplementary Table 2: Main effects and interactions for the analyzed hippocampal regions

Region	Fixed effects		
	Group	Time	Time-by-group interaction
Global			
Whole hippocampus	$F(1, 22.002) = 4.1, p = .055$	$F(3, 73.004) = 0.7, p = .533$	$F(3, 73.004) = 0.1, p = .960$
Subregions			
Head	$F(1, 22.003) = 5.5, p = .029$	$F(3, 73.006) = 0.4, p = .764$	$F(3, 73.006) = 0.9, p = .437$
Body	$F(1, 22.000) = 1.8, p = .190$	$F(3, 73.003) = 0.5, p = .679$	$F(3, 73.003) = 2.9, p = .041$
Whole tail	$F(1, 22.004) = 1.1, p = .312$	$F(3, 73.007) = 0.5, p = .680$	$F(3, 73.007) = 1.3, p = .275$
Subfields			
Left parasubiculum	$F(1, 21.998) = 0.5, p = .509$	$F(3, 73.011) = 1.3, p = .292$	$F(3, 73.011) = 0.4, p = .756$
Right parasubiculum	$F(1, 22.006) = 5.7, p = .025$	$F(3, 73.013) = 0.3, p = .820$	$F(3, 73.013) = 3.0, p = .037$
Left presubiculum head	$F(1, 22.003) = 0.1, p = .828$	$F(3, 73.007) = 1.4, p = .255$	$F(3, 73.007) = 1.2, p = .322$
Right presubiculum head	$F(1, 21.998) = 5.2, p = .033$	$F(3, 73.005) = 1.0, p = .391$	$F(3, 73.005) = 3.9, p = .012$
Left presubiculum body	$F(1, 22.004) = 2.3, p = .142$	$F(3, 73.009) = 1.1, p = .350$	$F(3, 73.009) = 0.5, p = .667$
Right presubiculum body	$F(1, 21.999) = 0.0, p = .936$	$F(3, 73.003) = 1.2, p = .159$	$F(3, 73.003) = 1.9, p = .145$
Left subiculum head	$F(1, 22.001) = 5.5, p = .029$	$F(3, 73.008) = 0.6, p = .612$	$F(3, 73.008) = 0.3, p = .845$
Right subiculum head	$F(1, 21.983) = 7.8, p = .011$	$F(3, 72.989) = 1.0, p = .401$	$F(3, 72.989) = 0.3, p = .793$
Left subiculum body	$F(1, 22.003) = 2.1, p = .164$	$F(3, 73.010) = 0.3, p = .832$	$F(3, 73.010) = 2.4, p = .073$
Right subiculum body	$F(1, 21.991) = 2.0, p = .174$	$F(3, 72.996) = 2.4, p = .075$	$F(3, 72.996) = 1.0, p = .398$
Left CA1 head	$F(1, 22.005) = 2.1, p = .160$	$F(3, 73.009) = 0.7, p = .572$	$F(3, 73.009) = 0.5, p = .680$
Right CA1 head	$F(1, 22.004) = 5.4, p = .030$	$F(3, 73.008) = 1.0, p = .403$	$F(3, 73.008) = 1.0, p = .402$
Left CA1 body	$F(1, 22.003) = 0.8, p = .379$	$F(3, 73.006) = 0.8, p = .507$	$F(3, 73.006) = 1.2, p = .330$
Right CA1 body	$F(1, 22.001) = 0.5, p = .484$	$F(3, 73.003) = 0.7, p = .584$	$F(3, 73.003) = 0.0, p = .990$
Left CA3 head	$F(1, 21.996) = 0.4, p = .544$	$F(3, 73.000) = 0.7, p = .588$	$F(3, 73.000) = 0.5, p = .680$
Right CA3 head	$F(1, 21.974) = 0.1, p = .755$	$F(3, 72.980) = 0.3, p = .804$	$F(3, 72.980) = 0.7, p = .564$
Left CA3 body	$F(1, 22.001) = 0.4, p = .517$	$F(3, 73.004) = 0.1, p = .945$	$F(3, 73.004) = 0.6, p = .634$
Right CA3 body	$F(1, 21.995) = 0.4, p = .532$	$F(3, 72.999) = 0.3, p = .805$	$F(3, 72.999) = 0.9, p = .455$
Left CA4 head	$F(1, 21.996) = 1.3, p = .273$	$F(3, 73.004) = 0.2, p = .922$	$F(3, 73.004) = 0.5, p = .667$
Right CA4 body	$F(1, 21.999) = 0.1, p = .830$	$F(3, 73.004) = 0.6, p = .606$	$F(3, 73.004) = 3.4, p = .002$

- Continued -

Supplementary Table 2 (continued)

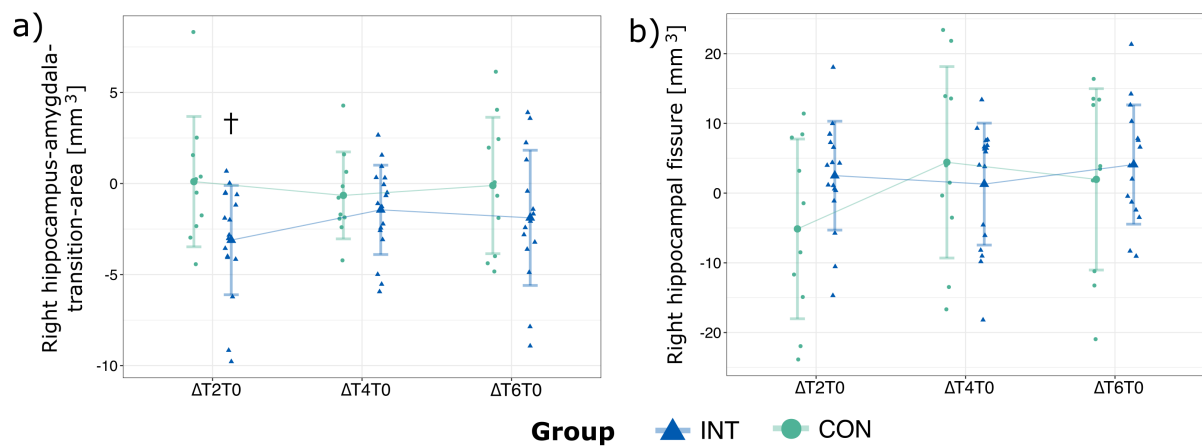
Region	Fixed effects		
	Group	Region	Group*time interaction
Subfields			
Left CA4 body	$F(1, 22.007) = 0.0, p = .924$	$F(3, 73.017) = 1.3, p = .276$	$F(3, 73.017) = 0.2, p = .875$
Right CA4 head	$F(1, 21.980) = 0.3, p = .583$	$F(3, 72.986) = 2.0, p = .116$	$F(3, 72.986) = 0.4, p = .793$
Left fimbria	$F(1, 22.016) = 4.1, p = .056$	$F(3, 73.029) = 1.5, p = .213$	$F(3, 73.029) = 0.3, p = .865$
Right fimbria	$F(1, 22.022) = 0.3, p = .574$	$F(3, 73.053) = 1.3, p = .292$	$F(3, 73.053) = 2.1, p = .103$
Left GC ML DG head	$F(1, 21.997) = 1.8, p = .197$	$F(3, 73.002) = 0.3, p = .815$	$F(3, 73.002) = 0.5, p = .677$
Right GC ML DG head	$F(1, 21.991) = 0.3, p = .569$	$F(3, 72.996) = 0.8, p = .489$	$F(3, 72.996) = 1.4, p = .239$
Left GC ML DG body	$F(1, 22.008) = 0.0, p = .977$	$F(3, 73.018) = 1.2, p = .310$	$F(3, 73.018) = 0.5, p = .705$
Right GC ML DG body	$F(1, 21.997) = 0.3, p = .608$	$F(3, 73.003) = 0.5, p = .693$	$F(3, 73.003) = 2.4, p = .074$
Left molecular layer HP head	$F(1, 22.003) = 3.2, p = .087$	$F(3, 73.007) = 0.1, p = .941$	$F(3, 73.007) = 0.3, p = .838$
Right molecular layer HP head	$F(1, 22.004) = 3.5, p = .077$	$F(3, 73.009) = 0.8, p = .505$	$F(3, 73.009) = 0.4, p = .730$
Left molecular layer HP body	$F(1, 22.003) = 1.4, p = .245$	$F(3, 73.008) = 0.4, p = .782$	$F(3, 73.008) = 2.4, p = .075$
Right molecular layer HP body	$F(1, 21.996) = 0.3, p = .611$	$F(3, 72.999) = 2.6, p = .059$	$F(3, 72.999) = 0.5, p = .676$
Left Hippocampus tail	$F(1, 22.005) = 0.9, p = .366$	$F(3, 73.009) = 0.0, p = .996$	$F(3, 73.009) = 2.2, p = .097$
Right Hippocampus tail	$F(1, 22.004) = 1.1, p = .317$	$F(3, 73.008) = 1.6, p = .183$	$F(3, 73.008) = 0.8, p = .508$
Left HATA	$F(1, 21.981) = 0.0, p = .869$	$F(3, 72.990) = 2.7, p = .053$	$F(3, 72.990) = 2.6, p = .058$
Right HATA	$F(1, 21.992) = 0.2, p = .647$	$F(3, 73.002) = 2.3, p = .080$	$F(3, 73.002) = 2.7, p = .051$
Left hippocampal fissure	$F(1, 21.983) = 0.1, p = .731$	$F(3, 73.005) = 1.5, p = .215$	$F(3, 73.005) = 2.1, p = .111$
Right hippocampal fissure	$F(1, 22.006) = 0.2, p = .648$	$F(3, 73.032) = 2.2, p = .100$	$F(3, 73.032) = 2.4, p = .071$
Exploratory			
Left entorhinal	$F(1, 21.928) = 0.0, p = .949$	$F(3, 72.967) = 0.3, p = .812$	$F(3, 72.967) = 0.9, p = .462$
Right entorhinal	$F(1, 21.918) = 3.0, p = .099$	$F(3, 72.980) = 1.8, p = .153$	$F(3, 72.980) = 0.7, p = .548$

Abbreviations: CA – Cornu ammonis. GC – Granular cells. HATA - Hippocampus-Amygdala-Transition-Area. HP – Hippocampus. ML – Molecular layer.

Supplementary Note 1: Additional results

Right Hippocampus-Amygdala-Transition-Area: Analysis revealed a strong trend for the interaction ($F(3,73.00)=2.71$; $p=0.051$), driven by a decrease in volume in the INT and no change in volume in the CON group from T0m to T6m (Supplementary Figure 1a). No further main effects (group or time) were observed. Post hoc analyses within group revealed a significant decrease from T0m to T2m in the INT ($t(16)=4.27$; $p=0.002$; $d=1.04$) and a trend decrease from T0m to T4m ($t(16)=2.43$; $p=0.082$; $d=0.59$). However, there was no significant difference between T0m and T6m in the INT group. In the CON group, no significant differences between time points was observed. Between-group comparisons for the change in volume ($\Delta T2T0$, $\Delta T4T0$, and $\Delta T6T0$) only revealed a trend for $\Delta T2T0$ ($t(25)=-2.50$; $p=0.058$; $d=-1.00$). Between-group comparisons for each time point separately (T0m, T2m, T4m, or T6m) did not reveal significant differences.

Right hippocampal fissure: Analysis revealed a trend for the interaction ($F(3,73.03)=2.44$; $p=0.071$), driven by an increase in both groups from T0m to T6m (Supplementary Figure 1b). No further main effects (group or time) were observed. Post hoc analyses revealed no further significant effects.



Supplementary Figure 1: Hippocampal subfields with trends in the group x time interaction. a) Right hippocampus-amygdala-transition-area and b) right hippocampal fissure. Presented are the delta values between T0m and T2m ($\Delta T2T0$), T0 and T4 ($\Delta T4T0$) as well as T0m and T6m ($\Delta T6T0$) for both, the intervention group (INT) and the control (CON) group, along with means and standard deviations (shown as error bars). † indicates within-group significance at $p < 0.05$. The data used to make the plots can be found in the Supplementary Data 1 file for this article.