

**DZNE**  
Deutsches Zentrum für  
Neurodegenerative Erkrankungen  
in der Helmholtz-Gemeinschaft

## Fail beautifully or how to learn from "failure"

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### The Hippocampus – Plastic and Vulnerable

- The formation of long-term memories for new events critically relies on the **Hippocampus** in the Medial Temporal Lobe

General Introduction

### Exercise related plasticity –The Hypothesis

- influence of aerobic exercise on neurovascular and structural hippocampal plasticity & related changes in memory

### Exercise Study in older adults

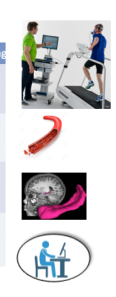
- intervention study with 40 elderly subjects (N=21, Nc=19)

Maass, Düzel, et al. (2015). *Molecular Psychiatry*

### Exercise Study in older adults

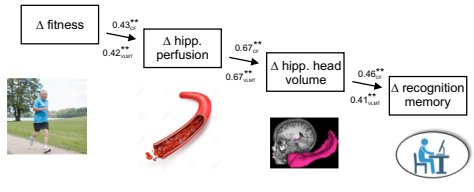
• **Methods overview (pre /post intervention)**

Target	Method	Parameter (pre and post training)
Fitness Level	Spiroergometry	Consumption of oxygen at Ventilatory Anaerobic threshold (VO <sub>2</sub> VAT)
Perfusion	3T Gadolinium contrast-based perfusion imaging	rCBF, rCBV in bilateral hippocampus & gray matter [ml/100g/min]
Hippocampal Structure	7T MRI (Manual segmentation on T1-weighted images)	Hippocampal Volume [cm <sup>3</sup> ] (head, body, tail, subfields)
Episodic Memory	Complex Figure Test (CF) Verbal learning and Memory Test (VLMT)	Early & Late Recall Recognition Memory (CF: high demands on pattern separation)



### Exercise Study in older adults

• Potential for vascular plasticity preserved in old age.




Maass, Düzel, et al. (2015), *Molecular Psychiatry*

### Follow up study

- Animal models: key role of [brain-derived neurotrophic factor \(BDNF\)](#), [insulin-like growth factor-1 \(IGF-1\)](#) and vascular endothelial growth factor (VEGF) in mediating exercise-induced structural and functional changes in the hippocampus.
- [platelet-derived growth factor-C \(PDGF-C\)](#) also shown to promote blood vessel growth and neuronal survival.



Growth factors	Blood sample (ELISA)	Concentration in serum [pg/ml]
		VEGF (Vascular endothelial growth factor)
		PDGF (Platelet-derived growth factor)
		BDNF (Brain-derived neurotrophic factor)
		IGF (Insulin-like growth factor)



→ Investigate relationships of peripheral growth factor levels with exercise-related changes in memory, hippocampal perfusion and volumes in older adults

### Results – Null results

- Growth factor levels were **not significantly** affected by exercise
- Growth factor levels changes were **not related** to changes in fitness or perfusion.

Concentration in serum [pg/ml]  
VEGF (Vascular endothelial growth factor)  
PDGF (Platelet-derived growth factor)  
BDNF (Brain-derived neurotrophic factor)  
IGF (Insulin-like growth factor)

### Null results – a failure ?

<https://www.nature.com/articles/s41562-019-0569->


Editorial | Published: 12 March 2019

#### The importance of no evidence

Nature Human Behaviour, 3, 197 (2019) | Cite this article  
7084 Accesses | 16 Citations | 168 Altmetric | Metrics

Publication bias threatens the ability of science to self-correct. It's time to change how null or negative findings are perceived and offer incentives for their publication.

At Nature Human Behaviour, we welcome the submission of studies reporting null or negative findings, provided that they address an important question of broad significance and are methodologically highly robust.



#### PUBLICATION BIAS

the tendency of authors or journals to prioritize for publication **positive findings**

### Results – Null results – published in Neuroimage

Randomized Controlled Trial | Neuroimage, 2016 May 1:131142-54.  
doi: 10.1016/j.neuroimage.2015.10.084. Epub 2015 Nov 3.

#### Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults

Anne Maass<sup>1</sup>, Sandra Düvel<sup>2</sup>, Tarja Brigandt<sup>3</sup>, Montique Goerke<sup>4</sup>, Andreas Becke<sup>5</sup>, Uwe Sobieray<sup>6</sup>, Katja Neumann<sup>6</sup>, Martin Lövdén<sup>7</sup>, Ulman Lindenberger<sup>8</sup>, Lars Bäckman<sup>9</sup>, Rüdiger Braun-Dullaeus<sup>10</sup>, Cläre Albrecht<sup>10</sup>, Hans-Jochen Heineke<sup>10</sup>, Wolfgang G Müller<sup>9</sup>, Volker Lesemann<sup>9</sup>, Michael Senthner<sup>10</sup>, Erwin Düssel<sup>10</sup>

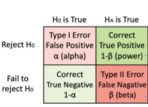
Affiliations & expand  
PMID: 26545456 DOI: 10.1016/j.neuroimage.2015.10.084  
Free article

#### Highlights

- Exercise-related changes in BDNF, IGF, VEGF and PDGF were measured in older adults
- Changes in hippocampal perfusion, volume (via 7 T MRI) and memory were assessed
- Fitness-related vascular hippocampal plasticity was not linked to growth factors
- Changes in IGF-1, hippocampal volume and memory were linked independent of exercise
- Potential reasons for negative findings and methodological shortcomings are discussed

### Methodological shortcomings /discussion

- Previous studies in older humans also not consistent
- methodological limitations
  - Markers not measured in brain
  - limitations of the **ELISA** kits/protocols used in this study
  - restriction to pre- and post-intervention measures
- low **power of this study** (0.7 and 0.6 to detect medium effects of exercise on fitness and GM perfusion) → **type II error high**
- future studies** should consider the time course by assessing short-term and long-term measures of growth factors, higher sample size



### The importance of null results

Anne Maass ✓  
Group Leader, DZNE  
Bestätigte E-Mail-Adresse bei dzne.de - Startseite  
Neuroscience Aging Memory Alzheimer's disease plasticity

TITEL	ZITIERT VON	JAHRE
Vascular hippocampal plasticity after aerobic exercise in older adults A Maass, S Düvel, M Goerke, A Becke, U Sobieray, K Neumann, ... Alzheimer's dementia 20 (1), 585-593	267	2015
Comparison of multiple tau-PET measures as biomarkers in aging and Alzheimer's disease A Maass, S Düvel, H Baker, A Hong, SK Loocher, W Lu, Jee, ... Neuroimage 137, 481-493	259	2017
Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults A Maass, S Düvel, T Brigandt, M Goerke, A Becke, U Sobieray, ... Neuroimage 121, 143-150	244	2016
Functional subregions of the human entorhinal cortex A Maass, D Bartsch, LA Lloyd, C Rangrahn, E Düzel Cereb Cortex 25(1), 60-69	195	2015
Strong evidence for pattern separation in human dentate gyrus D Berner, H Schütz, A Maass, A Carboni-Bianco, HJ Kauf, D Kumaran, ... Journal of Neuroscience 35 (28), 7859-7870	186	2015

### Some journal promote the publication of negative results

• **Brain Communications** (sister journal of Brain) publishes the following article types:

- Innovative, novel work within the scope of the journal
- Replication of important studies in the field including both direct replications of experiments and replications using different model systems
- **Well-substantiated, important negative results**
- Clinical trial reports

Thread

**Chris Chambers** @chamsc

"We don't publish negative results but our less prestigious sister journal will".

Terrible policy but worth noting that it just makes explicit the Ghetto Rule that operates for -ve results at other prestigious journals w/ "sisters".

eg J Neurosci vs eNeuro, Brain vs Brain Comms

**Rick Hasketa** @RHasketa · 19, May 2019

Editorial chief: Spoken with knowledge that his results are not even considered for Addictive Behaviors, seemingly not realizing how problematic that is. Offering a lower prestige alternative journal doesn't make that right.

Professor M. M. Spivey said:

"Articles that may not traditionally be considered by Addictive Behaviors, including methodological data papers, studies using smaller samples and cross-sectional designs, nonclinical studies, cross-cultural research, and case reports will be welcome in its sister journal Addictive Behaviors Reports."

Editor-in-Chief  
Professor M. M. Spivey  
London South Bank University

### Take home

- Null results/negative findings are as worth to be published as positive ones (well powered, robust methods)
- Even null findings due to methodological limitations can be valuable
- important for other researcher to prevent failure
- Poorly motivated or poorly executed research is not informative, regardless of the direction of the results.

