

# Abnormalities in task-fMRI activation are related to disease progression towards Alzheimer's disease

René Lattmann<sup>1,2</sup> | Niklas Vockert<sup>1</sup> | Judith Wesenberg<sup>2</sup> | Renat Yakupov<sup>1,3</sup> | Yanin Suksangkharn<sup>1</sup> | Hartmut Schütze<sup>2</sup> | Matthias Schmid<sup>4,5</sup> | Peter Dechent<sup>6</sup> | Klaus Fliessbach<sup>4,7</sup> | Daniel Janowitz<sup>8</sup> | Michael Ewers<sup>8</sup> | Michael T. Heneka<sup>7,9,10</sup> | Stefan Hetzer<sup>11</sup> | Oliver Peters<sup>12,13</sup> | Robert Perneczky<sup>14,15,16,17</sup> | Josef Priller<sup>13,18,19,20</sup> | Klaus Scheffler<sup>21</sup> | Anja Schneider<sup>4,22</sup> | Annika Spottke<sup>4,23</sup> | Katharina Buerger<sup>16,24</sup> | Christoph Laske<sup>25,26</sup> | Nina Roy-Kluth<sup>4</sup> | Stefan Teipel<sup>27,28</sup> | Jens Wiltfang<sup>29,30,31</sup> | Steffen Wolfsgruber<sup>9,32</sup> | Björn H. Schott<sup>29,33,34</sup> | Michael Wagner<sup>4,32</sup> | Frank Jessen<sup>4,35,36</sup> | Anne Maass<sup>1</sup> | Gabriel Ziegler<sup>1,3</sup> | Emrah Düzel<sup>1,3</sup>

<sup>1</sup>German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany

<sup>2</sup>Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University Magdeburg, Magdeburg, Germany

<sup>3</sup>Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany

<sup>4</sup>German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

<sup>5</sup>Institute of Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn, Germany

<sup>6</sup>MR-Research in Neurosciences, Georg-August-University Goettingen, Germany, Goettingen, Germany

<sup>7</sup>University of Bonn Medical Center, Bonn, Germany

<sup>8</sup>Institute for Stroke and Dementia Research (ISD), University Hospital, LMU, Munich, Germany

<sup>9</sup>German Centre for Neurodegenerative Diseases (DZNE), Bonn, Germany

<sup>10</sup>Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, Luxembourg, Luxembourg

<sup>11</sup>Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

<sup>12</sup>Charité – Universitätsmedizin Berlin, Berlin, Germany

<sup>13</sup>German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany

<sup>14</sup>LMU University Hospital, Munich, Germany

<sup>15</sup>Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

<sup>16</sup>German Center for Neurodegenerative Diseases (DZNE), Munich, Germany

<sup>17</sup>Department of Psychiatry and Psychotherapy, Klinikum der Ludwig-Maximilians Universität München, Munich, Germany

<sup>18</sup>Department of Psychiatry and Psychotherapy, Technical University of Munich, Munich, Germany

<sup>19</sup>University of Edinburgh and UK DRI, Edinburgh, UK

<sup>20</sup>Department of Psychiatry and Psychotherapy, Charité, Berlin, Germany

<sup>21</sup>University of Tübingen, Tübingen, Germany

<sup>22</sup>Department of Neurodegenerative Diseases and Geriatric Psychiatry, University of Bonn Medical Center, Bonn, Germany

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<sup>23</sup>Department of Neurology, University of Bonn, Bonn, Germany

<sup>24</sup>Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany

<sup>25</sup>German Center for Neurodegenerative Diseases (DZNE), Tuebingen, Germany

<sup>26</sup>Department of Psychiatry and Psychotherapy, University of Tuebingen, Tuebingen, Germany

<sup>27</sup>Department of Psychosomatic Medicine, University of Rostock, Rostock, Germany

<sup>28</sup>German Center for Neurodegenerative Diseases (DZNE), Rostock, Germany

<sup>29</sup>German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany

<sup>30</sup>Neurosciences and Signaling Group, Institute of Biomedicine (iBiMED), Department of Medical Sciences, University of Aveiro, Aveiro, Portugal

<sup>31</sup>University Medical Center Goettingen (UMG), Goettingen, Germany

<sup>32</sup>Department of Neurodegeneration and Geriatric Psychiatry, University Hospital Bonn, Bonn, Germany

<sup>33</sup>Leibniz Institute for Neurobiology, Magdeburg, Germany

<sup>34</sup>Department of Psychiatry and Psychotherapy, University Medical Center Goettingen (UMG), Göttingen, Germany

<sup>35</sup>Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany

<sup>36</sup>Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

#### Correspondence

René Lattmann, German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany.

Email: [rene.lattmann@dzne.de](mailto:rene.lattmann@dzne.de)

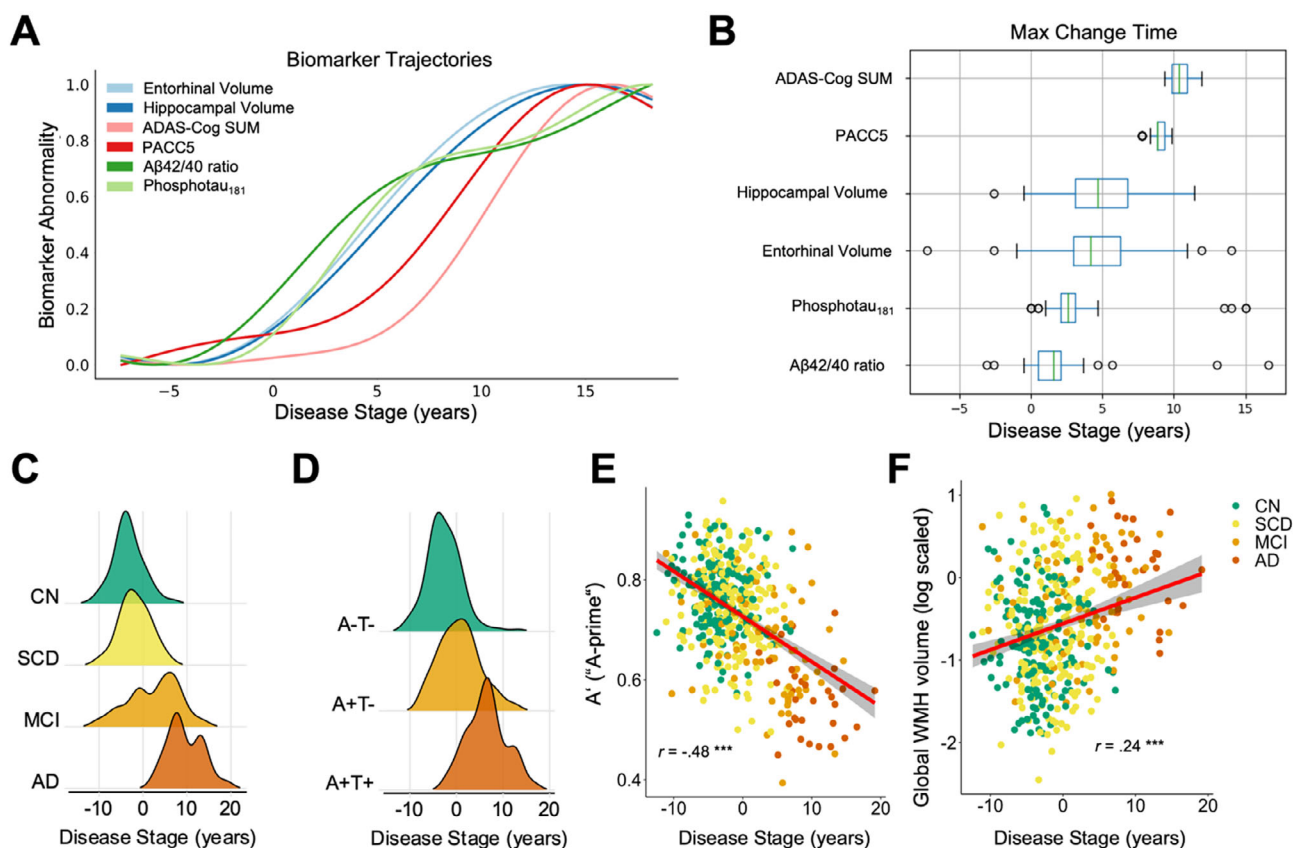
#### Abstract

**Background:** Differences in task-fMRI activation have recently been found to be related to neuropathological hallmarks of AD. However, the evolution of fMRI-based activation throughout AD disease progression and its relationship with other biomarkers remains elusive. Applying a disease progression model (DPM) to a multicentric cohort with up to four annual task-fMRI visits, we hope to provide a deeper insight into these relationships.

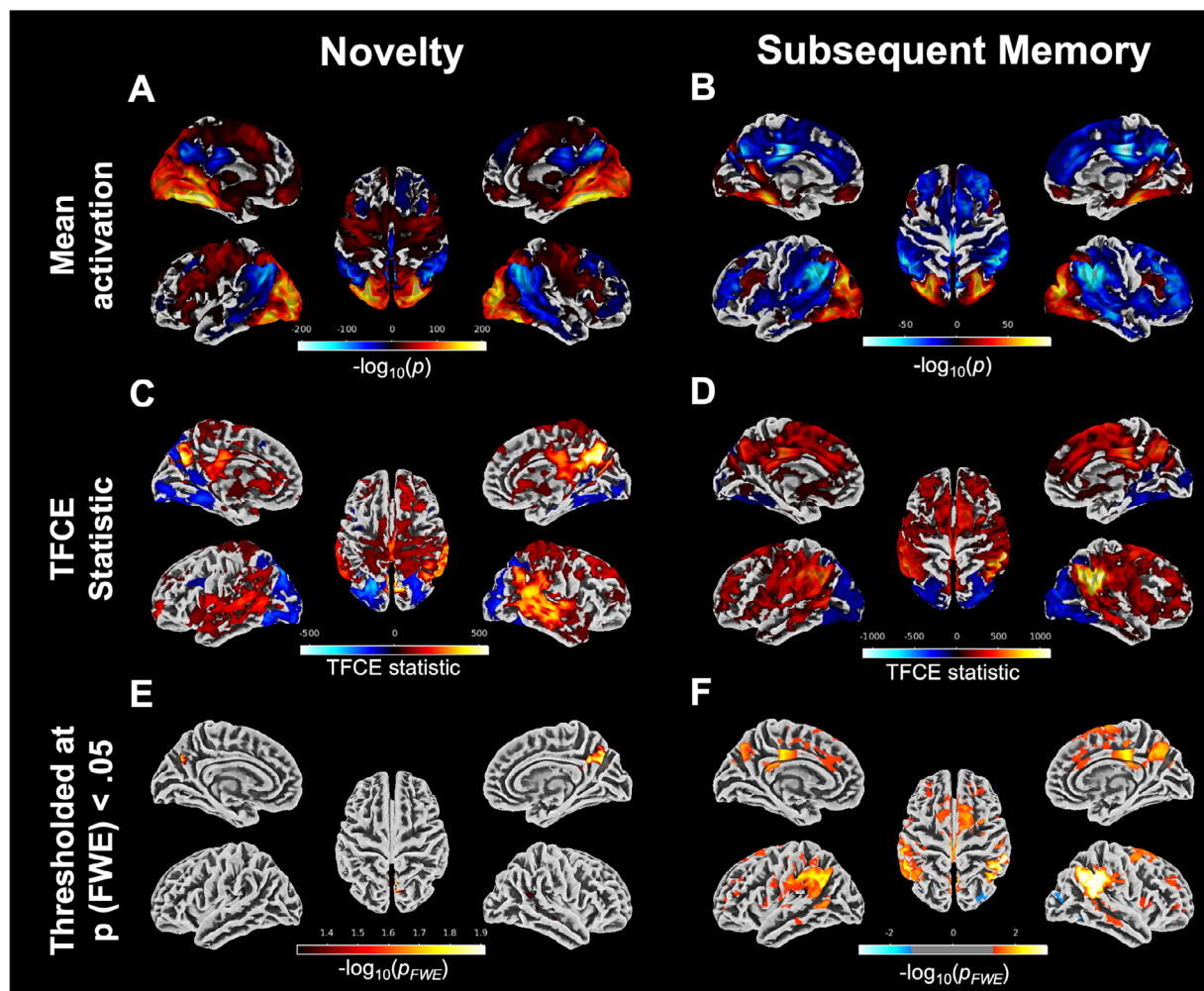
**Method:** We estimated AD disease stages using a multivariate Gaussian Process (GP) DPM including CSF-A $\beta$ 42/40 ratio, CSF-p-tau<sub>181</sub>, hippocampal and entorhinal volume, ADAS13-Cog sum and PACC5 scores. Disease stages from 493 participants with longitudinal task-fMRI measurements from DELCODE (165 healthy controls (CN), 214 participants with SCD, 82 with MCI, 32 with suspected AD) were obtained. We derived subsequent memory and novelty contrasts from a visual memory encoding task using general linear modeling (GLM). Contrasts from all available follow-ups were then submitted to voxel-based group-level GLM analyses. Activations from resulting disease-stage-related clusters were (1) used to estimate cluster-level trajectory curves over disease stages using smoothing splines and (2) submitted to linear-mixed effects models to test longitudinal changes over follow-ups.

**Result:** Our DPM-derived disease stages were associated with clinical groups, fMRI performance and white matter lesions (Figure 1C-F). Generally, in both contrasts, activation increases were observed in task-negative clusters while activation decreases were observed in task-positive clusters (Figure 2C-F). We did not find indications for inverted u-shaped associations between disease stage and activation in whole brain voxel-wise cross-sectional analyses. However, smoothing splines revealed non-linear monotonically increasing biomarker abnormality for task-negative areas, showing earliest changes towards the beginning of disease progression. After a plateau, fMRI activation increases in abnormality conjointly with volume changes. For task-positive areas, we observed linear relationships with disease stages (Figure 3). Activation changes over follow-ups were not associated with disease stages.

**Conclusion:** Biomarker abnormality timing in our DPM reflected hypothetical AD progression. Changes in task-fMRI activation and deactivation were both associated with progression towards AD. Smoothing spline fits indicated abnormality changes in task-fMRI activation to begin in the earliest phases of the disease. Findings can be discussed as differential pathophysiological processes such as complex reorganization and neural noise.

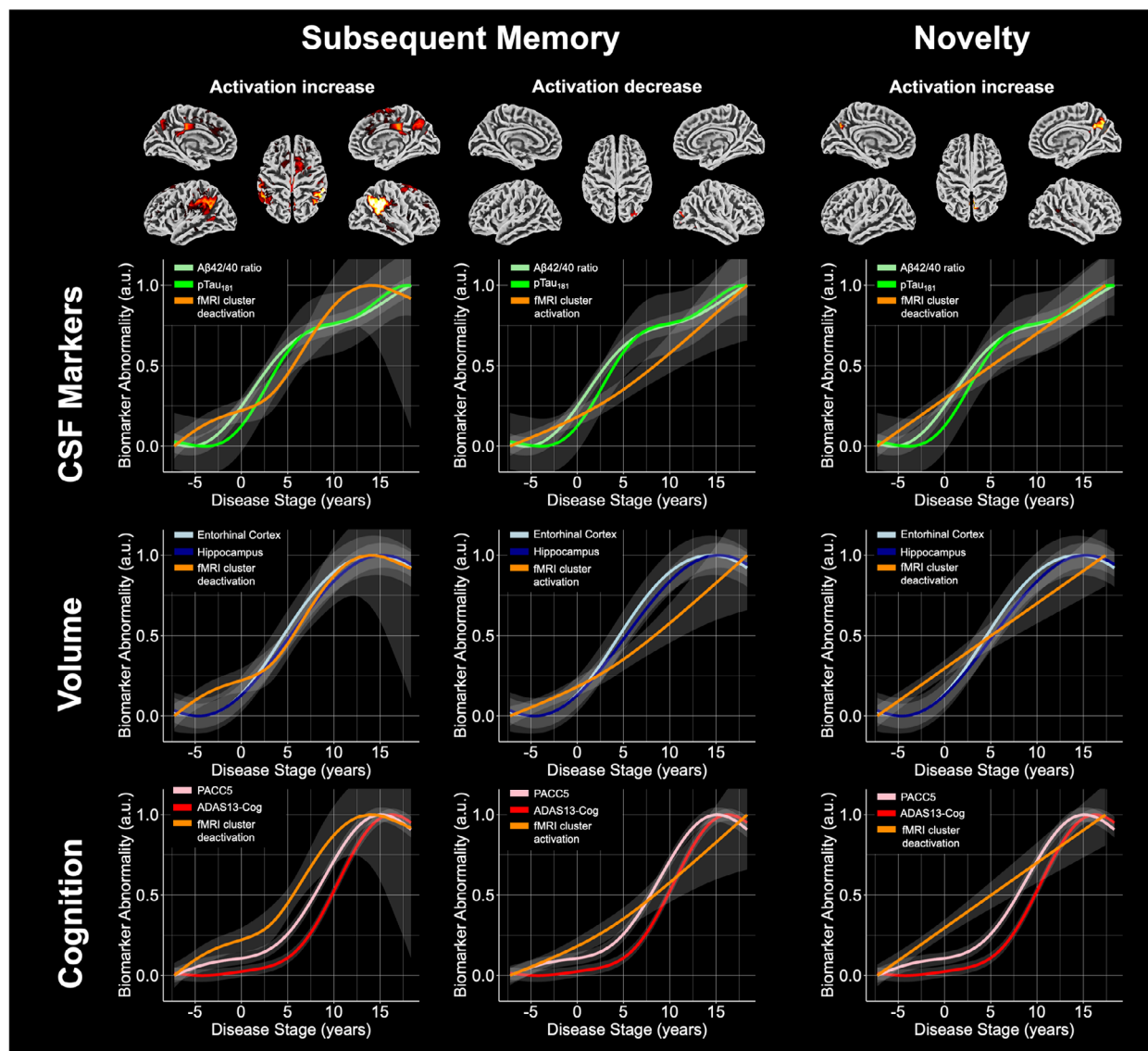


**Figure 1** Disease progression model used in this study and association with clinical groups and covariates. **A** GP-based DPM used in this study comprising longitudinal CSF, volumetric MRI, and cognition data from the DELCODE cohort using 787 available data points. **B** Maximum change timing of biomarker curves from the model posterior. Strongest change of biomarkers first for CSF, followed by volumetric MRI and finally cognition. **C** Disease stage differences between different diagnostic groups. **D** Disease stage differences between AT subgroups. A-T- exhibit the earliest disease stages, whereas A+T+ make up the group with the largest disease stages. Participants with biomarker profile A-T+ were excluded prior to the analysis. **E** Associations between the disease stage residualized for age, sex, and education and the association with memory performance during the task-fMRI session. **F** Association between the covariates adjusted disease stage and global white matter hyperintensities volume. \*\*\* =  $p < .001$ , \*\* =  $p < .01$ , \* =  $p < .05$ , n.s. =  $p > .05$



**Figure 2**  $-\log_{10}$  p-value maps for the associations between contrast maps and disease stage in surface representation. **A** Mean contrast value across all participants and scans in the general linear model using the sandwich estimator toolbox (intercept) for novelty. Widespread activations (red) in lingual gyri, occipital and prefrontal cortex. Deactivations (blue) are seen in the precuneus, posterior cingulate cortex, inferior parietal lobule, as well as temporal and frontal cortices. **B** Mean contrast value for the subsequent memory effect. Deactivations are seen in precuneus, cingulate cortex, as well as temporal and frontal cortices. Activations are mainly seen in lingual and parahippocampal gyri, as well as occipital regions. **C** Unthresholded map of the Threshold-free cluster enhancement (TFCE) statistic for novelty. Mainly deactivated regions exhibit positive relationships with disease stage, whereas activated regions show negative associations. **D** Unthresholded map of the TFCE statistic for the subsequent memory effect. Here, similar observations as in C apply. Thresholded map of C using family wise error (FWE) correction. Bilaterally, only positive associations survive correction in the precuneus. **F** FWE thresholded map of D.





**Figure 3** Disease trajectory curves for fMRI biomarkers overlaid with biomarker groups from the disease progression model (see Figure 1). First and third column show increases in abnormal activation for task-negative regions (regions with less activation during task than rest; i.e. “deactivation” regions). Second column highlights observed activation decreases in task-positive regions (regions with more activation during task than rest). First row shows the clusters from Figure 2E-F. Below, biomarker curves for CSF biomarkers (second row), volumes (third row) and cognition (fourth row) are overlaid with estimated fMRI biomarker curves for the respective clusters. For fMRI biomarkers, prediction  $\pm 1.95 \times \text{SE}$  confidence bands are plotted. For the Gaussian Process DPM, mean  $\pm$  standard deviation values are shown. fMRI biomarkers are among the earliest changes of abnormalities seen in our sample.