# Beyond Diagnosis: A Longitudinal, Better-Than-Expected Approach to the Neural Correlates of Resilience

Vincent Hammes[1,2], Katharina Brosch[1,2,3], Paula Usemann[1,2], Friederike David[1,4], Frederike Stein[1,2], Florian Thomas-Odenthal[1,2], Lea Teutenberg[1,2], Susanne Meinert[5], Janik Goltermann[5], Kira Flinkenflügel[5] , Julia Hubbert[5] , Tiana Borgers[5] , Judith Krieger[5], Elisabeth Leehr[5], Linda Bonnekoh[5,6], Dominik Grotegerd[5], Tim Hahn[5], Benjamin Straube[1,2], Hamidreza Jamalabadi[1,2], Udo Dannlowski[4], Igor Nenadić[1,2], Robert Miller[8], Andreas Jansen[1,2,9], Tilo Kircher[1,2] & Nina Alexander[1,2]

[1] Department of Psychiatry and Psychotherapy, University of Marburg, Marburg, Germany, [2] Center for Mind, Brain and Behavior, University of Marburg, Marburg, Germany, [3] Institute of Behavioral Science, Feinstein Institutes for Medical Research, Glen Oaks, USA, [4] Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany, [5] Institute of Translational Psychiatry, University of Münster, Germany [6] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany, [7] Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, Germany [8] Psychological Methodology, Psychological University Berlin, Am Köllnischen Park 2, 10179 Berlin, Germany, [9] Core-Facility BrainImaging, Faculty of Medicine, Philipps-Universität Marburg, Marburg, Germany

## BACKGROUND

Resilience constitutes the ability to adapt positively to adversity and is shaped by the interplay of **multiple biological and environmental risk** and protective factors. Consequently, a positive and **resilient outcome** needs to be operationalized with respect to **interindividual differences** in risk, diathesis and protective factors.

Resilience has been associated with **specific morphometric alterations** in gray matter volume (GMV) and cortical thickness:

**a) larger GMV** in the **medial prefrontal cortex** (mPFC) and **hippocampi**, and
**b) greater cortical thickness** of the mPFC[1-5].

This study extends previous research by addressing the following **limitations**:

**multi-system risk**

Previous studies largely focus on single risk factors

↓

Integrating multiple risk and protective factors

**resilience operationalization**

Previous studies are based on diagnosis (dichotomous categorization of healthy vs. diagnosis)

↓

Implement „better-than-expected“ operationalization

↓

Dimensional approach to disentangle diagnosis- and resilience-based effects

Resilience is a mental health outcome that does not exclude psychopathological symptoms but is simply better than expected, given one's individual cumulative risk!

**Aims of this study**

A) Operationalize resilience as a „better-than-expected“ outcome in depressive symptom severity relative to individual cumulative risk.

B) Investigate brain structural correlates of resilience over multiple time points.

## METHODS

### Sample

**N=1804 depressed** (MDD, SKID I) and **healthy** (HC) central-european individuals from the FOR2107 cohort[6]. Age 18-65, Ø 35.2 years, 65% female.

### Risk and protective factors

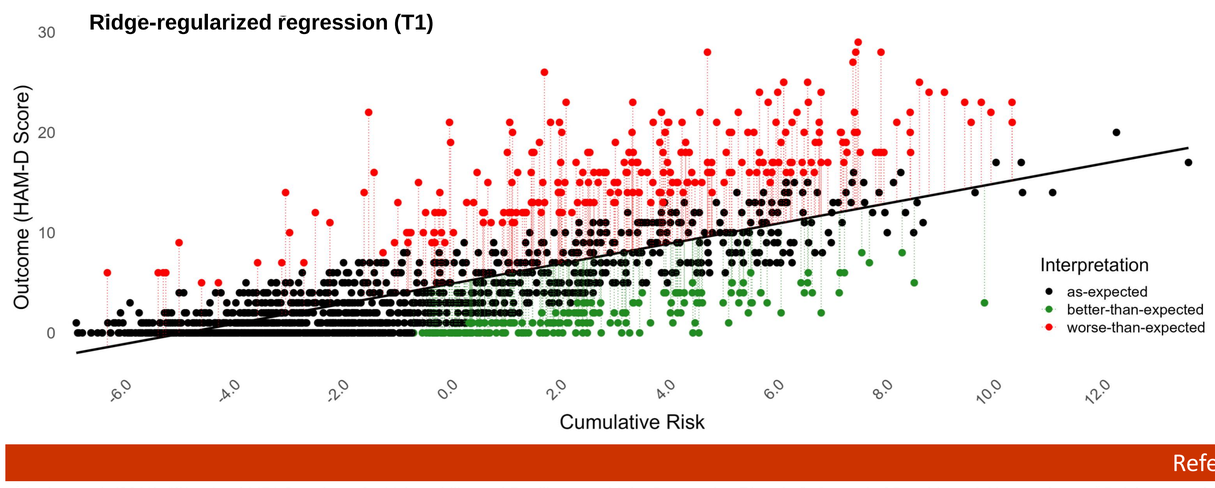
| Table 1 | Assessment | Risk | Protective |
|---|---|---|---|
| Familial risk (affective/psychotic disorder) | Self-report | X | |
| Intelligence | MWT-B | X | X |
| Trait extraversion | NEO-FFI | X | X |
| Trait neuroticism | NEO-FFI | X | X |
| Trait openess | NEO-FFI | X | X |
| Trait agreeableness | NEO-FFI | X | X |
| Trait conscientiousness | NEO-FFI | X | X |
| Attachment style | RSQ | X | X |
| Childhood trauma | CTQ, ACE | X | |
| Stressful life events (positive/negative) | LEQ | X | X |
| Perceived stress | PSS | X | X |
| Immigration | Self-report | X | |
| Social Support | F-SozU, Self-report | X | X |
| Education | Self-report | X | X |
| Income | Self-report | X | X |

### Statistical Framework

Using the Hamilton Depression Rating Scale (**HAM-D**) as a dimensional outcome measure, we applied **ridge-regularized regression** analysis to **predict symptom severity** by multiple risk and protective factors (Table 1) in the full sample of N=1804 at T1 and 2-year follow-up (T2; N=808).

Model fit T1: regularization parameter $\lambda_{SD}$ = 4.1, **deviance ratio of 51.4%** (refers to the explained variance of the model). Model fit T2: $\lambda_{SD}$ = 5.7, **deviance ratio of 44.2%**. Residual scores showed moderate stability over time ($r$=0.31, $p$<0.001).

**Residual** scores reflect the **individual deviation** of actual and predicted HAM-D score. Thresholding at the standard residual error (SD = 4.18), we identified **n=208 resilient** (-1SD, better-than-expected) and **n=251 vulnerable** (+1SD, worse-than-expected) individuals at T1, alongside **n=200 as-expected** individuals (minimal residuals).




## METHODS

### Brain Morphometry

**Groups** were compared regarding differences in **GMV** and **cortical thickness** using voxel-based and surface-based analyses. Additionally, **residual scores** were used to **predict GMV** and **cortical thickness at T1 and T2** (regression analysis, full sample).

Based on prior studies, confirmatory **region-of-interest (ROI)** analyses and exploratory **whole-brain** analyses were conducted (ROIs: hippocampus, mPFC). **Sensitivity analyses** were conducted with lifetime diagnosis (MDD) as covariate.

## RESULTS

### Clinical Characteristics

| Table 2 | ***As Expected*** (*n*=200) | ***Resilience*** (*n*=208) | ***Vulnerability*** (*n*=251) | Group comparison |
|---|---|---|---|---|
| Age | 33.1 (12.2) | 34.8 (12.5) | 35.4 (13.6) | *p*=0.142 |
| Sex (*n* female, %) | 129 (65%) | 131 (66%) | 167 (67%) | *p*=0.726 |
| MDD diagnosis (*n*, %) | 59 (30%) | 128 (62%) | 232 (92%) | ***p*<0.001**[a] |
| Remission (in MDD, acute/partial/full) | 18 / 12 / 41 | 19 / 41 / 68 | 181 / 37 / 13 | ***p*<0.001**[b] |
| Duration of illness (months) | 33.0 (44.6) | 33.0 (41.3) | 50.5 (67.2) | ***p*=0.016**[c] |
| HAM-D sum score | 2.8 (3.3) | 1.5 (1.8) | 16.3 (4.5) | ***p*<0.001**[d] |
| HAM-D score predicted | 2.8 (3.2) | 7.2 (2.0) | 8.3 (3.2) | ***p*<0.001**[e] |
| GAF score | 85.1 (14.2) | 78.1 (14.6) | 57.9 (12.9) | ***p*<0.001**[f] |
| RS-25 sum score | 139.2 (22.3) | 113.7 (22.9) | 102.9 (26.9) | ***p*<0.001**[f] |

[a] association with *As Expected* and *Vulnerability*; [b] association with all levels in *Resilience* and *Vulnerability*, and with full and acute remission in *As Expected;* [c] *Vulnerability* > *Resilience;* [d] *Vulnerability* > *Resilience, As Expected* and *As Expected* > *Resilience*, [e] *Vulnerability* > *Resilience*, *As Expected* and *Resilience* > *As Expected;* [f] *As Expected* > *Resilience*, *Vulnerability* and *Resilience* > *Vulnerability.*

### Brain Morphometry: Cross-Sectional (T1)

**Regression Analyses (N=1804)**

- No significant association between residual score (=resilience) and GMV or cortical thickness across all models (ROI and whole-brain, sensitivity analyses).

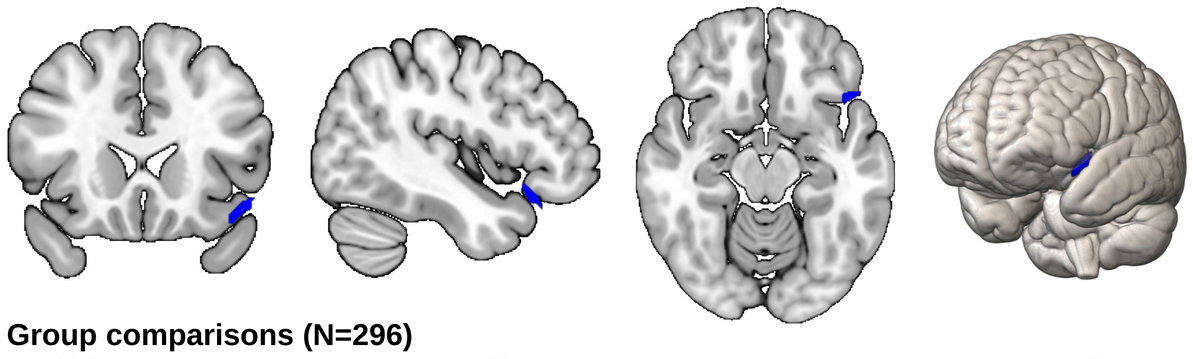
**Group comparisons (N=659)**

- No differences in GMV or cortical thickness between groups across all models (ROI and whole-brain, sensitivity analyses).

### Brain Morphometry: Longitudinal (T2)

**Regression Analyses (N=808)**

- **Higher resilience at T1 predicted lower GMV** in the left inferior orbitofrontal gyrus **at T2** (lIOFG, $k$=172, $p_{FWE}$=0.006, x/y/z=–48/20/–12).
- Similar in ROI and whole-brain design, comparable results in sensitivity analyses.
- **Resilience at T1 did not predict cortical thickness** at T2.



**Group comparisons (N=296)**

- GMV and cortical thickness at T2 from individuals of extreme groups at T1 was compared (*n*=95 *Resilience*, *n*=97 *Vulnerability*, *n*=104 *As Expected*).
- *Resilience* < *Vulnerability:* lower GMV in a small cluster within the lIOFG at T2, similar to regression analysis ($k$=32, $p_{FWE}$=0.023, x/y/z=–48/20/–14).

## DISCUSSION

- This study examined cross-sectional and longitudinal brain structural correlates of resilience beyond diagnostic categories, using a **data-driven** “**better-than-expected**” **approach** in a large adult sample.
- We did **not replicate** previous findings of larger GMV or cortical thickness in the hippocampus or mPFC associated with resilience[1–5]. Cross-sectionally, no structural differences related to resilience were observed. Longitudinally, however, **resilience at T1 predicted lower GMV** in the left inferior orbitofrontal gyrus (lIOFG) **at T2**.
- These longitudinal findings support the concept of “**skin-deep resilience**”—adaptive functioning under adversity that may be accompanied by biological cost[7].
- Interpretation remains limited by the **bidirectional relationship between depression and resilience**, particularly regarding the timing of HAM-D assessments.

## CONCLUSION

This is the first study to investigate brain structural correlates of resilience (beyond diagnosis) employing a residual approach in a large, heterogeneous sample.

While resilience to specific risk factors might be associated with greater GMV or cortical thickness, resilience to cumulative risk in a design that accounts for diagnosis-based effects did not present a neural signature cross-sectionally, but rather predicted smaller GMV in the lIOFG in a 2-year follow-up.

## References

[1] Amico et al. (2011). “Structural MRI Correlates for Vulnerability and Resilience to Major Depressive Disorder”. *Journal of Psychiatry & Neuroscience.* [2] Bolsinger et al. (2018). “Neuroimaging Correlates of Resilience to Traumatic Events—A Comprehensive Review”. *Frontiers in Psychiatry*. [3] Burt et al. (2016). “Structural Brain Correlates of Adolescent Resilience*”. Journal of Child Psychology and Psychiatry.* [4] Moreno-López et al. (2020). “The Resilient Emotional Brain: A Scoping Review of the Medial Prefrontal Cortex and Limbic Structure and Function in Resilient Adults With a History of Childhood Maltreatment”. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. [5] Schmaal et al. (2017). “Cortical Abnormalities in Adults and Adolescents with Major Depression Based on Brain Scans from 20 Cohorts Worldwide in the ENIGMA Major Depressive Disorder Working Group”. *Molecular Psychiatry*. [6] Kircher et al. (2019). “Neurobiology of the major psychoses: a translational perspective on brain structure and function—the FOR2107 consortium*”. European archives of psychiatry and clinical neuroscience*. [7] Brody et al. (2013). “Is Resilience Only Skin Deep? Rural African Americans’ Preadolescent Socioeconomic Status-Related Risk and Competence and Age 19 Psychological Adjustment and Allostatic Load”. *Psychological science.*

Contact: Vincent Hammes, M.Sc., University of Marburg, vincent.hammes@uni-marburg.de