Effects of Psychotherapy on Glutamatergic Neurotransmission

Wade-Bohleber, Laura ; Zoelch, Niklaus ; Lehmann, Mick ; Ernst, Jutta ; Richter, Andre ; Seifritz, Erich ; Boeker, Heinz ; Grimm, Simone

Abstract: Introduction: Psychodynamic psychotherapy is an effective and widely used treatment for major depressive disorder (MDD); however, little is known about neurobiological changes associated with induced symptom improvement. Methods: Proton magnetic resonance spectroscopy with a two-dimensional J-resolved sequence served to test the relationship between glutamate (Glu) and glutamine (Gln) levels, measured separately in pregenual anterior cingulate cortex (pgACC) and the anterior midcingulate cortex (aMCC) as a control region, with change in depression symptoms after 6 months of weekly psychodynamic psychotherapy sessions in MDD patients. Depressed (N = 45) and healthy (N = 30) subjects participated in a baseline proton magnetic resonance spectroscopy measurement and a subgroup of MDD subjects (N = 21) then received once-a-week psychodynamic psychotherapy and participated in a second proton magnetic resonance spectroscopy measurement after 6 months. Change in depression symptoms was assessed using the Hamilton Depression Rating Scale (HAMD). Results: Higher pretreatment pgACC Gln concentrations in MDD patients compared to healthy controls were associated with symptom severity. Patients and controls did not differ regarding Gln levels in aMCC nor regarding Glu levels in both regions. The association of pgACC Gln concentration and severity of depressive symptoms was reversed after 6 months of psychotherapy in MDD subjects. Regarding Gln in aMCC as well as Glu in both regions, there were no significant associations with improvement of depressive symptoms in the course of psychotherapy. Discussion: Findings indicate specific regional effects of psychodynamic psychotherapy on glutamatergic neurotransmission and thereby highlight the key role of the pgACC in both depression pathophysiology and recovery.

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Laura Wade-Bohleber[a, b] Niklaus Zölch[a, c] Mick Lehmann[a] Jutta Ernst[a] André Richter[d] Erich Seifritz[a] Heinz Boeker[a] Simone Grimm[a, e, f]

[a]Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric University Hospital Zurich, University of Zurich, Zurich, Switzerland; [b]Psychological Institute, Zurich University of Applied Sciences, Zurich, Switzerland; [c]Department of Forensic Medicine and Imaging, Institute of Forensic Medicine, University of Zurich, Zurich, Switzerland; [d]Department of Consultation-Liaison-Psychiatry and Psychosomatic Medicine, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [e]Medical School Berlin, Berlin, Germany; [f]Department of Psychiatry, Charité Campus Benjamin Franklin, Berlin, Germany

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Psychotherapy · Depression · Proton magnetic resonance spectroscopy · Glutamate · Glutamine

Abstract
Introduction: Psychodynamic psychotherapy is an effective and widely used treatment for major depressive disorder (MDD); however, little is known about neurobiological changes associated with induced symptom improvement. ***Methods:*** Proton magnetic resonance spectroscopy with a two-dimensional J-resolved sequence served to test the relationship between glutamate (Glu) and glutamine (Gln) levels, measured separately in pregenual anterior cingulate cortex (pgACC) and the anterior midcingulate cortex (aMCC) as a control region, with change in depression symptoms after 6 months of weekly psychodynamic psychotherapy sessions in MDD patients. Depressed ($N = 45$) and healthy ($N = 30$) subjects participated in a baseline proton magnetic resonance spectroscopy measurement and a subgroup of MDD subjects ($N = 21$) then received once-a-week psychodynamic psychotherapy and participated in a second proton magnetic resonance spectroscopy measurement after 6 months. Change in depression symptoms was assessed using the Hamilton Depression Rating Scale (HAMD). ***Results:*** Higher pretreatment pgACC Gln concentrations in MDD patients compared to healthy controls were associated with symptom severity. Patients and controls did not differ regarding Gln levels in aMCC nor regarding Glu levels in both regions. The association of pgACC Gln concentration and severity of depressive symptoms was reversed after 6 months of psychotherapy in MDD subjects. Regarding Gln in aMCC as well as Glu in both regions, there were no significant associations with improvement of depressive symptoms in the course of psychotherapy. ***Discussion:*** Findings indicate specific regional effects of psychodynamic psychotherapy on glutamatergic neurotransmission and thereby highlight the key role of the pgACC in both depression pathophysiology and recovery.

Introduction

Even though psychotherapy has been proven as a highly effective treatment for patients with major depressive disorder (MDD) [1] and is recommended by treatment

karger@karger.com
www.karger.com/nps

Correspondence to:
Laura Wade-Bohleber, laura.wade-bohleber@uzh.ch

guidelines for MDD [2], little is known about neurobiological changes associated with induced symptom improvement. The pregenual anterior cingulate (pgACC) is a brain region where aberrant and restored function, respectively, have been associated with both acute MDD symptoms and symptom improvement after treatment with antidepressants, ketamine, and electroconvulsive therapy [3–6]. The investigation of this region also appears promising regarding glutamatergic neurotransmission. Glutamatergic metabolites play a major role in the pathophysiology of MDD and have been linked to symptom improvement [9, 31, 32, 35]. However, findings on the role of glutamatergic metabolites in MDD treatment remain inconsistent, which might at least be partially related to the investigation of brain regions less clearly associated with depression and small sample sizes. Further, glutamate (Glu) and glutamine (Gln) are often measured together as Glx, possibly disguising a specific role of Glu and Gln for symptom improvement in MDD. Glu is the major excitatory neurotransmitter in the human brain and increased extracellular Glu has been associated with excitotoxicity and impaired synaptic integrity that might eventually lead to functional and structural abnormalities as observed in MDD [7]. Gln is the principal metabolite of synaptic Glu, directly related to Glu levels in the synaptic cleft and discussed as having neuroprotective properties [8].

It has been proposed that psychotherapy promotes synaptic plasticity and thereby also eventually results in metabolite changes. Abdallah et al. [9] reported a robust association between reductions in occipital cortex (OCC) Glu levels and treatment response after 12 weeks of cognitive-behavioral therapy (CBT) in depression. Regarding brain regions more relevant for the pathophysiology of MDD, a study by O'Neill et al. [10] reported effects of CBT on glutamatergic neurotransmission in the anterior midcingulate cortex (aMCC). Here, however, patients with obsessive-compulsive disorder (OCD) were investigated, and Glu and Gln were measured together as Glx. Both studies examined the effects of CBT. Effects of psychodynamic psychotherapy, an effective and widely used treatment for depression [11, 12], on glutamatergic neurotransmission remain to be defined. Hence, in this innovative study, we used proton magnetic resonance spectroscopy to investigate the relationship between Glu and Gln levels, measured separately in pgACC and a control region (aMCC), with change in depressive symptoms after 6 months of weekly psychodynamic psychotherapy sessions in MDD patients. We hypothesized that Glu and Gln levels in pgACC, but not aMCC, would be inversely associated with pretreatment symptom severity and improvement after psychotherapy, respectively.

Materials and Methods

Subjects were eligible for study participation if they were between 18 and 65 years of age and presented no history of substance abuse/dependence or psychotic disorder. Advertisements using flyers, university mailing lists, and local internet platforms served to recruit individuals interested in participating in the study. In addition, individuals with depression were referred for study participation by local psychiatrists and psychologists. For depressed subjects, a primary ICD diagnosis of depression determined inclusion. Psychotropic medication was allowed but had to be stable for at least 4 weeks prior to study enrollment. Healthy subjects had to present neither a current psychiatric disorder nor a history of MDD. All participating subjects provided written informed consent. Subjects participated in a baseline MRS measurement and a subgroup of MDD subjects then received outpatient psychodynamic psychotherapy at a frequency of approximately once a week and participated in a second MRS measurement after 6 months. Psychodynamic psychotherapy was provided by trained psychotherapists affiliated with two local psychoanalytic institutes. A two-dimensional J-resolved sequence [15, 16] was used to evaluate metabolic levels in the pgACC and aMCC (Fig. 1a–c; online suppl. Table S1; online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000530312). Change in depression symptoms was assessed using the Hamilton Depression Rating Scale (HAMD) [13]. Pretreatment differences in Glu and Gln between healthy and depressed subjects were assessed using linear regression with metabolites as dependent and group (depressive vs. healthy), depressive symptoms (HAMD score), and medication status as independent variables. Pre- to posttreatment changes in Glu and Gln over time dependent on depressive symptoms (HAMD score) were assessed using linear mixed models (LMMs) with random intercepts. Glu and Gln served as dependent variables and time, depressive symptoms (HAMD), their interaction (time*HAMD) as independent variables. Medication and number of psychotherapy sessions were added as control variables but omitted from the final LMM if they were not significant. Code supporting the described analyses is available in the supplemental materials. The corresponding data files are available here: https://doi.org/10.48573/kfpv-pt95.

Results

Baseline Analysis

Table 1 provides details on the sociodemographic variables of the final sample. A Wilcoxon signed-rank test indicated that age was not different between healthy (Mdn = 27.55, IQR = 11.60) and depressed (Mdn = 26.96, IQR = 8.10) subjects, $p = 0.81$. Gender was not unequally distributed between groups (χ^2 [1, N = 75] = 0.03, p = 0.87). Cramer-Rao lower bounds provided by ProFit were used as an estimate for the reliability and quality of the data. Cramer-Rao lower bounds for Gln (pgACC: median = 9.9, min: 5.5, max: 97.2; aMCC: median = 8.1, min = 4.8, max = 27.5) and Glu (pgACC: median = 1.8, min: 1.2, max:

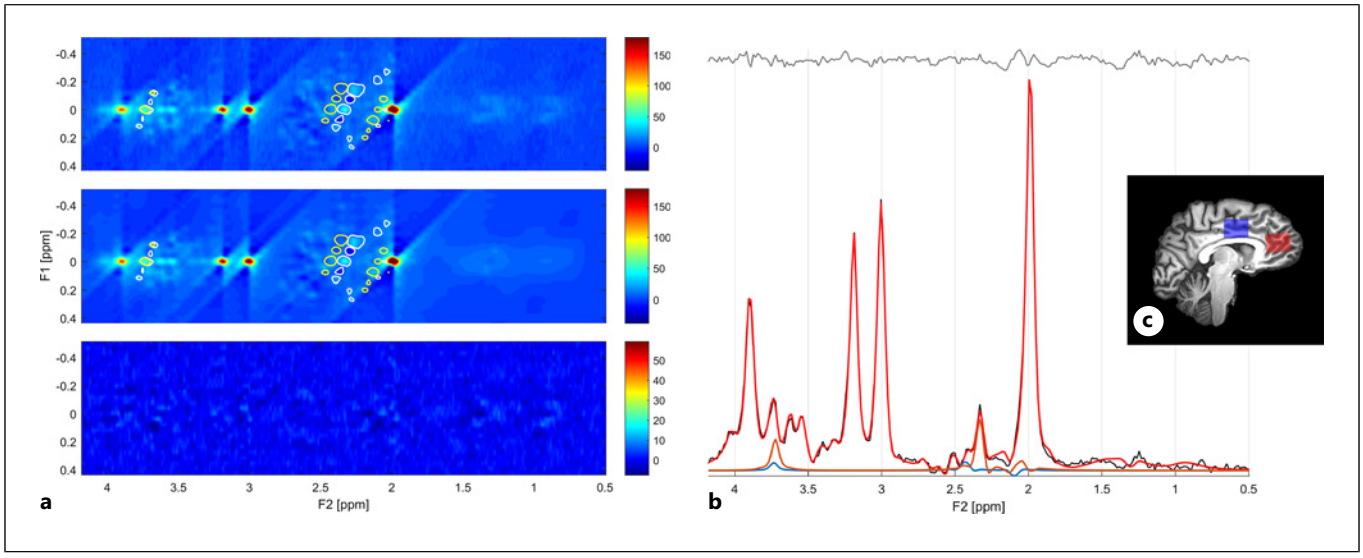

Fig. 1. a Two-dimensional JPRESS spectrum with the measured spectrum on top, the fitted spectrum in the middle, and the residuals (measured spectrum – fitted spectrum) at the bottom. Yellow circles indicate regions of Gln peaks, and white circles indicate regions of Glu peaks. **b** Cross-sectional view of the two-dimensional JPRESS spectrum along *F*1 = 0. The measured spectrum (black), the fit (red), and the residuals (gray) on top are plotted. In addition, the contributions from Gln (blue) and Glu (orange) are shown. **c**. Voxel placement in the pgACC (red) and aMCC (blue).

3.3; aMCC: median = 1.3, min = 1.0, max = 3.5) were comparable to previous studies [14], and no significant differences between groups were observed.

At baseline, depressed subjects showed higher Gln levels than healthy subjects in pgACC (cf. Fig. 2a). Regression results are reported in Table 2. There were no group differences in Gln levels in the aMCC (cf. online suppl. Table S2). Further, there were no group differences in Glu levels neither in the pgACC nor aMCC (cf. online suppl. Tables S3, S4).

Pre- to Posttreatment Analysis

LMMs revealed a significant interaction for time and depressive symptoms (timepoint*HAMD) for Gln levels in the pgACC (Table 3). There was an inverse association of depressive symptoms and Gln post- compared to pretreatment: pretreatment, a higher HAMD score was associated with lower Gln levels, while posttreatment, a higher HAMD score was associated with higher Gln levels (Fig. 2b). We observed no association neither with medication status nor with the number of psychotherapy sessions (cf. online suppl. Table S5). Posttreatment, responders to treatment (n = 11), defined with ≥50% reduction in depressive symptoms (HAMD score), showed significantly lower pgACC Gln levels (M = 0.22, SD = 0.1) than partial or non-responders (n = 10, M = 0.32, SD = 0.06), t (19) = 2.87, $p < 0.05$. We found no changes over time in Gln in the aMCC (cf. online suppl. Table S6). Moreover, we observed no changes over time in Glu neither in the pgACC nor in the aMCC (cf. online suppl. Tables S7, S8).

Discussion

To the best of our knowledge, this is the first study investigating the relationship of both Glu and Gln levels in pgACC and aMCC, as a control region, with change in depression symptoms after 6 months of weekly psychodynamic psychotherapy sessions in MDD patients. Results show that higher pretreatment pgACC Gln concentrations in MDD patients compared to healthy controls were associated with symptom severity. Patients and controls did not differ regarding Gln levels in aMCC nor regarding Glu levels in both regions. The association of pgACC Gln concentration and severity of depressive symptoms was reversed after 6 months of psychotherapy in MDD subjects. Regarding Gln in aMCC as well as Glu in both regions, there were no significant associations with improvement of depressive symptoms in the course of psychotherapy.

We focused our investigation of glutamatergic neurotransmission on the pgACC, given extensive evidence linking its aberrant and restored function, respectively, to MDD overall symptom severity, rumination, reduced

Table 1. Sociodemographics and clinical characteristics of the sample

	Healthy	Depressed	
		pretreatment	posttreatment
	(*n* = 30)	(*n* = 45)	(*n* = 21)
Sex, *n* (%)			
Female	24 (80.0)	34 (75.6)	17 (81.0)
Male	6 (20.0)	11 (24.4)	4 (19.0)
Age, years	30.95±10.62	30.69±10.96	29.92±10.92
Missing, *n* (%)	0 (0)	1 (2.2)	0 (0)
HAMD	0.69±0.97	15.88±3.52	9.29±6.74*
Missing, *n* (%)	1 (3.3)	2 (4.4)	0 (0)
Psychotropic medication, *n* (%)			
Medicated	0 (0)	12 (26.7)	8 (38.1)
Unmedicated	30 (100%)	33 (73.3%)	13 (61.9%)
Number of PT sessions			28.34±12.08

HAMD, Hamilton Depression Rating Scale; PT, psychotherapy. *There was a significant reduction in depressive symptoms from pre- to posttreatment, t (20) = 5.17, $p < 0.001$. Of 21 depressed subjects receiving psychotherapy, 15 showed moderate depression (HAMD scores 17–23) and 6 mild depression (HAMD scores 8–16) pretreatment. Posttreatment, 3 showed moderate depression, 8 mild depression, and 10 no depression (HAMD scores 0–7). Using criteria of 50% symptom decrease for full response and 25% for partial response from pre- to posttreatment, 11 subjects responded to treatment, 6 partially responded, and 4 did not respond.

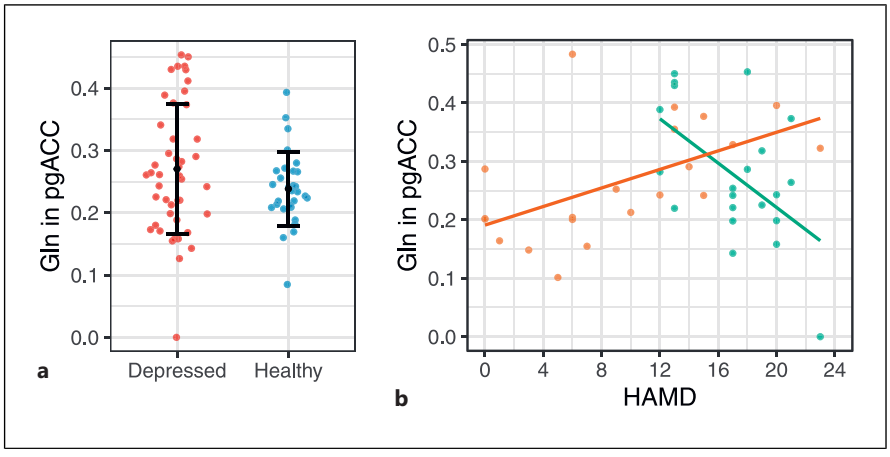

Fig. 2. a Group difference in Gln in pgACC between depressed and healthy subjects. **b** Association of Gln and HAMD in pgACC pre- and posttreatment in depressed subjects. Green: pretreatment, orange: posttreatment.

control over emotional responses as well as to symptom improvement after treatment with antidepressants, ketamine, and electroconvulsive therapy [3, 5, 6, 15, 16]. The aMCC was selected as a control region as it plays a role in disparate aspects of emotion processing, i.e., it is crucial for the integration of sensory input and emotional arousal as well as for the perception and anticipation of pain [17, 18]. Furthermore, following their differential regional receptor fingerprints, Gln and Glu concentrations have been shown to differ in pgACC and aMCC [19, 20].

Chronic stress and depression have been associated with alterations in glutamatergic neurotransmission, including an increase in Glu, which could lead to excitotoxicity and impaired synaptic integrity, thereby contributing to the functional and structural brain changes observed in MDD [7]. Gln levels have been suggested as an index of glutamatergic neurotransmission [21–23]. Gln is largely found in glia where it is produced by Gln synthetase, on Glu taken up from the synapse into glia [24, 25]. The uptake of Glu and its conversion to Gln is

Table 2. Regression results using Gln in pgACC at T1 as the criterion

	Estimates	SE	t	CI: 2.5%	CI: 97.5%
Intercept	−0.57**	0.21	−2.73	−0.98	−0.15
Group	1.01**	0.34	3.00	0.34	1.68
HAMD	−0.81*	0.33	−2.45	−1.47	−0.15
Medication	−0.24	§0.17	−1.43	−0.58	0.10

$R2 = 0.14$, $F(3, 68) = 3.58$, $p = 0.02$. Group reference category: healthy subjects. Medication reference category: unmedicated. *Indicates $p < 0.05$. **Indicates $p < 0.001$.

Table 3. LMM results using Gln in pgACC at T1 and T2 as the criterion

	Estimates	SE	t	CI: 2.5%	CI: 97.5%
Intercept	0.38*	0.13	2.97	0.13	0.62
Time	−0.30*	0.12	−2.43	−0.54	−0.06
HAMD	−1.18**	0.28	−4.15	−1.72	−0.64
Time*HAMD	1.52**	0.30	5.02	0.94	2.10
Random effects					
	Variance	SD			
Subject	0.13	0.36			
Residual	0.06	0.24			

HAMD, Hamilton Depression Rating Scale. *Indicates $p < 0.05$. **Indicates $p < 0.001$. Number of observations: 42, subjects: 21. Time reference category: pretreatment.

one of the main mechanisms by which Glu excitotoxicity is prevented and is critically dependent on glial function. Even though results are not consistent, several recent studies and meta-analyses reported increased Gln levels in MDD patients [26–30]. Interestingly, in agreement with our findings, some of these studies also found no differences in Glu in MDD compared to healthy controls [27, 28] and reported an association between depression severity and Gln but not Glu levels [27, 31]. Conversely, Gln increase has been observed after ketamine treatment in patients with MDD, mirroring the antidepressant response [32]. One might argue that our results might therefore also be interpreted as an effect of antidepressants since some patients also received medication. However, medication status was included as a covariate in all analyses and showed no associations with Gln or Glu. Therefore, it seems more likely that our findings rather reflect a neuroprotective Gln response to cellular dysfunction [8]. Another explanation might be a compensatory mechanism of glial hypertrophy and increase in Gln to Glu astrocyte conversion [33]; however, this is only a speculative interpretation lacking direct evidence.

Glutamatergic metabolites have also been linked to symptom improvement, and it has been suggested that modulation of glutamatergic neurotransmission might represent a shared biological pathway [34, 35]. However, several longitudinal studies failed to detect longer term changes in Glu or Glx in MDD patients following extended treatment with antidepressants [36–39]. By contrast, increased Glu and Glx levels in pgACC have been associated with response following extended courses of both electroconvulsive therapy [40, 41] and repetitive transcranial magnetic stimulation [42].

To our knowledge, only a handful of prior studies have investigated the effects of psychotherapy on glutamatergic neurotransmission. Abdallah et al. [9] investigated the OCC in MDD patients prior to and after a course of 12 weeks of weekly CBT and reported that subjects with the greatest reductions in Glu levels had the largest reductions in depression severity. However, the OCC has a limited role in the pathophysiology of MDD, and hence differences in its neurotransmitter levels may not be mechanistically relevant. Similarly, changes in OCC Glu levels associated with symptom improvement may not be directly related to psychotherapy. During the course of psychodynamic psychotherapy, dysfunctional patterns of experiencing oneself and one's environment are identified, contextualized, and worked through in the context of the therapeutic relationship, resulting in more adaptive regulation of emotions and cognitions. Thereby, psychotherapy may promote synaptic plasticity and these changes in plasticity may result in metabolite changes such as those observed here in a region involved in the pathophysiology of MDD, i.e., pgACC, but not aMCC. These observations align with the fact that glutamatergic neurotransmission in the pgACC underpins emotion regulation [43]. Along that line, a study by O'Neill et al. [44] in pediatric patients with OCD showed that 12–14 weekly CBT sessions were associated with a significant reduction in pgACC Glu concentration. Interestingly, a recent study in OCD reported Glx increases rather than decreases in dorsal ACC in patients with comorbid mood disorders [45], thereby again underlining regional variations of glutamatergic metabolites. Alternatively, one might assume differential short- and long-term effects of psychotherapy, as patients were measured after receiving only 4 sessions of exposure therapy.

There are several limitations to this study. We investigated younger patients suffering from mild to moderate depression. It has been suggested that different profiles of glutamatergic abnormality occur during illness course, with high concentrations in the early illness phase being followed by lower levels as a result of neurotoxic effects [25, 46]. Also, our sample included medicated patients; however, we included medication status as a covariate in our analyses and found no associations with Gln or Glu.

To conclude, the current study shows for the first time consequences of psychodynamic psychotherapy on glutamatergic neurotransmission. Findings indicate specific regional effects, i.e., an association between pgACC Gln concentration and symptom improvement and thereby highlight the key role of the pgACC in antidepressant effects.

Acknowledgments

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Statement of Ethics

This study was approved by the Ethics Commission of the canton of Zurich, Switzerland. The reference number is KEK-ZH-Nr. 2011-0298. Written informed consent was obtained from all study participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Laura Wade-Bohleber: investigation, formal analysis, visualization, funding acquisition, writing – original draft, and writing – review and editing. Niklaus Zölch: formal analysis, software, and writing – review and editing. Mick Lehmann: data curation, formal analysis, and writing – review and editing. Jutta Ernst: investigation and writing – review and editing. André Richter: writing – original draft and writing – review and editing. Erich Seifritz: resources, supervision, and writing – review and editing. Heinz Boeker: supervision, funding acquisition, project administration, and writing – review and editing. Simone Grimm: conceptualization, supervision, writing – original draft, and writing – review and editing.

Data Availability Statement

Data supporting the findings reported in this article are accessible here: https://doi.org/10.48573/kfpv-pt95. The R code supporting the statistical analyses is available in the supplemental material. Further inquiries can be directed to the corresponding author.

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