Research article

Modulation of respiration pattern variability and its relation to anxiety symptoms in remitted recurrent depression

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A B S T R A C T

Background: Depression is related to default mode network (DMN) connectivity and higher respiration pattern variability (RPV). In addition, DMN connectivity and RPV are interrelated and predict a poorer clinical course of depression. The association of RPV and depression might further be boosted by anxiety levels. Aim of the present study was to investigate whether a mindfulness-based training in emotionally challenged remitted depressed participants (rMDD) leads to reduced DMN connectivity and lower RPV, and if RPV interacts with anxiety levels.
Methods: To challenge participants, sad mood was induced with keywords of personal negative life events in 49 rMDD during fMRI before and after a 4-week mindfulness-based attention training (MBAT) or progressive muscle relaxation. Respiration was measured by means of a built-in respiration belt.
Results: After both trainings, rMDD showed no significant changes in DMN connectivity. However, MBAT was effective in reducing the RPV which was related to lower anxiety levels especially in high anxious individuals.
Conclusions: RPV can be influenced by training which may hint to an underlying biological pathway of training effects. Importantly, these effects seem to be associated with anxiety levels. Therefore, respiration focused training might be an important tool assisting the treatment of depression and anxiety.

1. Introduction

Acutely higher respiratory variability in reaction to anxious or otherwise stressful stimuli is a biologically adequate response and will resolve after some time (e.g. Guyon et al., 2020). In contrast, longer lasting high respiration pattern variability (RPV) instead of regular deep abdominal breathing is considered maladaptive and seems related to psychological problems (Asnaashari et al., 2012; Vlemincx et al., 2013). Recently, we could demonstrate that remitted recurrent depressed individuals show a significantly different respiration pattern with higher variability compared to matched healthy controls. Here, altered RPV parameters were linked to daily mood and worse outcome after 3 years (Zamoscik et al., 2018). Further, RPV parameters were associated with connectivity of the parahippocampal gyri with the posterior cingulate cortex (PCC), which is part of the default mode network (DMN; Zamoscik et al., 2018). Increased PCC-parahippocampal connectivity has also

previously been linked to worse outcome (Zamoscik et al., 2014). Additionally, the importance of the parahippocampus during sad mood in depression has recently been replicated for chronically ill patients (Renner et al., 2017) thereby pointing to a target region/target connectivity for interventions.

In studies with healthy volunteers it could be demonstrated that mindfulness induction or meditation might positively influence both the DMN (Taylor et al., 2013) and the RPV (Vlemincx et al., 2013). Additionally, guided breathing has been shown to have positive effects on anxiety (Wannemueller et al., 2016; Yamada et al., 2017). The effects of breathing on anxiety might act via sympathetic nerve activity, arterial baroreflex sensitivity (Fonkoue et al., 2018), and chemoreflex sensitivity (Narkiewicz et al., 2006). Since anxiety is frequently comorbid with depression (Tiller, 2013) and related to altered breathing (Kato et al., 2017; Klorman et al., 1975), it might be an important factor in the association of RPV and mood. Recently, in a larger cohort of children with

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major depression, an anxious subtype was identified showing e.g. increased suicidal ideation even in the absence of a fully formed comorbid anxiety disorder (Haberling et al., 2019). Further, more comorbid anxiety disorders were related to a poorer outcome in depressed individuals in a 10-year follow-up study (Hung et al., 2019). In sum, there is evidence pointing to a significant role of anxiety in depression, with respiration being one possible important contributing factor. As yet, no study has analyzed the possible changes of RPV via training and its interrelations with anxiety in depression.

The present analyses aimed at exploring the impact of brief trainings (mindfulness-based attention and progressive muscle relaxation as active control) on RPV, PCC – parahippocampal connectivity, and the influence of RPV on anxiety in participants with remitted recurrent depression. We expected lower PCC – parahippocampal connectivity after training. Additionally, we anticipate lower RPV after the mindfulness training which includes a short breath focus compared to control without a breath focus, and we will address this via exploratory analyses. All positive changes on the biological level (e.g. a more natural/lower RPV) should be associated with lower anxiety levels or even predict them.

2. Methods

Data were collected between 8/2014 and 3/2017 in Mannheim, Germany.

In a randomized controlled trial, we collected data of 55 individuals with remitted recurrent depression (rMDD) with at least 2 previous major

depressive episodes and not fulfilling depression criteria for at least 2 months prior to study entry. All participants completed a 4-week manual-based training of mindfulness-based focused attention (MBAT) including mindfulness of breath and body scan (with some breathing related aspects and further exercises without breathing aspects; as shown above, mindfulness was found to alter RPV and DMN in healthy individuals: Vlemincx et al., 2013; Taylor et al., 2013) or progressive muscle relaxation (PMR, active control, parallelised for time and attention; chosen because it is well established, patients can profit from it, and it is easily adaptable for durations; e.g. Goksin and Ayaz-Alkaya, 2020; Nasiri et al., 2018) to improve depression symptoms. Sessions in both trainings followed the same formal schedule with psychoeducational introduction (both: coping with difficulties during practice; MBAT: mindful awareness and automatic pilot; PMR: basic principles of PMR), review of homework, introduction and practice of elements (both: demonstration and practicing of short exercises for application during daily life; MBAT: practice of focused attention mindfulness elements; PMR: practice of relaxation elements with muscle tension for different body regions for about 5s followed by relaxation for about 35s), debriefing and homework assignment. The trainings were carried out by supervised cognitive behavioral psychologists or mindfulness-based stress reduction trainers (MBSR trainers had completed a formal 1.5-year professional MBSR training, all trainers had several years of experience in regularly teaching mindfulness skills to patients with mental illness) held once per week (50min, 5 individual sessions) plus audio-guided daily homework (20min/day).

Table 1. Demographic, clinical and RPV characteristics of the sample.

	mean ± SD			p value (Cohens f)
	All	PMR	MBAT	PMR vs MBAT
n	49	25	24	
sex: female/male	32/17	16/9	16/8	.844[a]
age [years]	38.51 ± 10.66	39.24 ± 11.70	37.75 ± 9.66	.630[b] (0.07)
education: CSE or high school diploma/A levels	15/34	7/18	8/16	.686[a]
age of illness onset [years]	22.01 ± 10.41	23.20 ± 11.61	20.72 ± 9.02	.415[b] (0.12)
number of depressive episodes	4.61 ± 2.68	4.16 ± 2.39	5.08 ± 2.92	.231[b] (0.18)
average length of previous depressive episode [weeks]	33.85 ± 46.66	40.56 ± 50.58	26.57 ± 41.86	.304[b] (0.15)
time since remission [weeks]	154.08 ± 167.28	192.40 ± 201.61	112.43 ± 109.35	.098[b] (0.25)
previous inpatient treatment (%(n))	41 (20)	48 (12)	33 (8)	.296[a]
current psychotropic medication[c] (%(n))	17 (8)	24 (6)	8 (2)	.155[a]
WHO5 pre [%]	53 ± 22	53 ± 24	54 ± 21	.992[b] (0.00)
WHO5 post [%]	58 ± 20	55 ± 25	62 ± 14	.294[b] (0.17)
homework compliance [%]	92 ± 1	89 ± 1	95 ± 1	.066[b] (0.27)
BAI pre	9.03 ± 10.47	9.31 ± 9.91	8.75 ± 11.22	.854[b] (0.03)
BAI post	7.32 ± 7.04	7.09 ± 6.62	7.58 ± 7.60	.812[b] (0.03)
PD CV pre	0.74 ± 0.30	0.63 ± 0.30	0.84 ± 0.26	.011[b] (0.39)
PD CV post	0.72 ± 0.24	0.74 ± 0.25	0.70 ± 0.24	.556[b] (0.08)
Number of bins pre	23.67 ± 22.13	18.76 ± 15.64	28.79 ± 26.71	.114[b] (0.23)
Number of bins post	21.33 ± 16.15	22.28 ± 17.71	20.33 ± 14.65	.678[b] (0.06)

[a] Chi^2 test.
[b] univariate ANOVA.
[c] medication (including n = 2 participants with multiple prescriptions; n = 1 person with missing value).
selective serotonin reuptake inhibitor (SSRI): n = 4.
serotonin-norepinephrine reuptake inhibitor (SNRI): n = 2.
noradrenergic and specific serotonergic antidepressant (NaSSA): n = 1.
atypical antidepressant norepinephrine-dopamine reuptake inhibitor (NDRI): n = 1.
atypical antidepressant agomelatine: n = 1.
atypical antipsychotic quetiapine: n = 1.
melatonin: n = 1.
Intervention: PMR: progressive muscle relaxation; MBAT: mindfulness-based focused attention training; pre/post: pre/post intervention.
CSE: Certificate of Secondary Education, 8 years (2 still at school).
Questionnaires: WHO5: well-being index, percentage of quality of life; BAI: Beck anxiety inventory.
Respiratory features: RPV: respiration pattern variability; PD CV: expiratory pause duration coefficient of variance; number of bins: number of respiratory frequency bins above 10% threshold of the main respiration rate derived from Welch's power spectral density estimates.

The participants included into the present analyses are also included in the paper by Timm et al. (2018) who additionally recruited a set of participants for which no fMRI and respiration measures were taken. Participants were matched for age and sex between intervention groups and randomized to the groups (allocation 1:1 by number list). Two participants of the PMR group said that they would have preferred to be in the MBAT group. While this may have had an impact on the effort put into completing the homework, the time spent doing homework, which was our measure of compliance, was very good for the whole sample (Table 1). Post intervention data of four participants were missing (3 quit the study during intervention (2 MBAT, 1 PMR), one had a longer stay at a health resort so it was not feasible to include post data within 3 months post intervention (participant out of MBAT group)) and during two post measurements we had equipment problems resulting in data loss. The final data set includes 49 participants (mean age 39 years, 32 females; 25 PMR, 24 MBAT; Table 1). Two participants fulfilled the criteria for generalized anxiety disorder and nine for partially remitted other anxiety disorders: four for social phobia, three for agoraphobia, and two for specific phobias according to the structured clinical interview for DSM-IV (SCID I; Wittchen et al., 1997) which was applied by trained clinical psychologists. Exclusion criteria were bipolar and psychotic disorders, substance dependence, current substance abuse, current obsessive-compulsive, posttraumatic stress, and eating disorders as well as contraindications for the fMRI (including hypertension, heart disease and surgeries and other severe illnesses like COPD or cancer) as well as current psychotherapy. Participants who took psychotropic medication were on a stable dose for at least 2 months prior to the intervention with an agreement to inform us if they had to change dosage until the follow-up (no one had to change). Non-psychotropic medication (if any; drug named most was the contraceptive pill) was used with a stable dose at least for one year.

Participants also filled in questionnaires about well-being and anxiety (WHO5 wellbeing index: https://www.psykiatri-regionh.dk/who-5/Pages/default.aspx; Bech et al., 2003; Beck anxiety inventory/BAI: Beck et al., 1988). The WHO5 was used to assess self-reported quality of life. For some analyses regarding anxiety, we split the sample into low (BAI score ≤ 15; n = 32; 16 participants MBAT, 16 PMR) and high (BAI score ≥ 16; n = 17; 8 MBAT, 9 PMR) anxiety subgroups. The higher anxiety subgroup included all participants with BAI scores of 16 or above and/or a diagnosis of generalized anxiety disorder or a partially remitted anxiety disorder at pretest (mean BAI scores 4.73 ± 3.88 vs. 17.13 ± 13.89). Precisely, to be included into the higher anxious subgroup, at least one of two criteria had to be met: 1) at least moderate anxiety symptoms (BAI score 16 or higher; Beck and Steer, 1993), and 2) suffering from an anxiety disorder which was no more than partially remitted at the time of pretest.

Pre and post intervention, participants completed a 4.5 min sad mood induction phase during fMRI with keywords of three negative personal life events (1.5min each) and atmospheric music (for a more detailed description of the paradigm see supplement and Zamoscik et al., 2014) on a 3T Trio Tim MRI Scanner (Siemens Healthineers, Erlangen, Germany). We sampled respiration cycle and heart rate at 50Hz with built-in equipment (PMU Wireless Physio Control, Siemens Healthineers, Erlangen, Germany). Pre-processing of data acquired during sad mood induction as well as first and second level analyses followed a standard procedure as described in the supplemental material and Zamoscik et al. (2018). Seed region for connectivity analyses was the PCC (10mm sphere around MNI coordinates -7,-45,24; see supplement for more details). Four cases were excluded from fMRI analyses due to altered physiological parameters (falx meningioma with impact on normalization; thrombosis diagnosis after inclusion; heterotopia of grey matter) or missing triggers in the physiology files.

Therefore, we had complete fMRI data from 45 participants: 24 in the PMR group and 21 in the MBAT group.

For respiration analyses we used MATLAB R2017a (The MathWorks Inc., Natick, USA) and calculated Welch's power spectral density estimates (variable: number of respiratory frequency bins above 10% threshold of the main respiration rate) as well as the coefficient of variance (CV) of the expiratory pause duration (PD). For this, we calculated the slope of the respiration curve at a window size of five samples with a cut-off of two. Clusters of minimum peaks were used to determine rough temporal markers for a provisional pause onset, which was then recursively extended into both directions based on the slope parameters to determine pause onset and offset (like in Zamoscik et al., 2018). Finally, two RPV parameters were calculated: number of bins and PD CV. For both parameters, higher values indicate higher RPV which we relate to maladaptive respiratory behavior when expressed over a longer time period and not only in direct response to stressful stimuli.

Statistical analyses for all analyses except fMRI were performed with IBM SPSS 25 (SPSS Inc., Chicago, Illinois, USA), effect sizes were calculated with G*Power 3.1.9.2 (Faul et al., 2007). We used Chi^2 tests, GLMs, correlations, and regression analyses to test group differences and intervention effects. For the two GLMs (rmANCOVAs) focusing on the intervention effect we used age and sex as covariates as possible factors influencing respiration and anxiety (e.g. Hinz et al., 2019; Sheel et al., 2016). For an additional analysis, we also included baseline PD CV values as those were significantly different between groups pre intervention. As sex had a significant effect in one rmANCOVA, we included sex also in the regression analyses. In those regression analyses, we aimed at predicting post BAI scores with the reduction in RPV (PD CV change score, bins change score; change scores were calculated via subtracting pre from post scores) via intervention while accounting also for pre BAI scores. Including homework compliance as covariate did not change the pattern of results.

The study was approved by the local ethics committee of the University of Heidelberg and conformed to the Declaration of Helsinki. All participants gave written informed consent.

3. Results

After both trainings, rMDD participants showed no significant change in DMN connectivity with the PCC as seed and the parahippocampus as ROI on a $p < .05$ FWE corrected threshold. Further, they also showed no significant change in DMN connectivity at $p < .05$ (FWE corrected whole-brain cluster level).

In an rmANCOVA, MBAT had a significant positive effect on expiratory PD variance (lower RPV: F(1,45) = 11.64, $p = .001$, f = .51, covariate sex: F(1,45) = 4.25, $p = .045$, f = .31; corrected for baseline PD CV: F(1,44) = 3.78, $p = .058$, f = .29, covariate sex: F(1,44) = 1.01, $p = .321$, f = .15) compared to PMR (group*intervention effect). Furthermore, in a second rmANCOVA MBAT seemed to have a positive effect on the number of respiratory frequency bins compared to PMR, but this was not significant (fewer bins/lower RPV: F(1,45) = 3.67, $p = .062$, f = .28).

In rMDD participants with higher anxiety, higher RPV (number of bins) was related to higher anxiety pre intervention ($r = .62$, $p = .004$; Figure 1). Further, reduced BAI scores through intervention tended to be associated with decreased number of bins but the correlation did not reach significance ($r = .39$, $p = .060$). This association could not be found in low anxiety participants ($r = .02$, $p = .463$). There were no such associations with PD CV (low anxiety: $r = -.19$, $p = .146$; high anxiety: $r = .16$, $p = .271$).

In the regression analyses on post BAI scores with RPV parameters (accounted for pre BAI scores and sex), the model was significant only for the MBAT group (corrected R^2 = .42, F(4,18) = 5.03, $p = .007$; PMR:
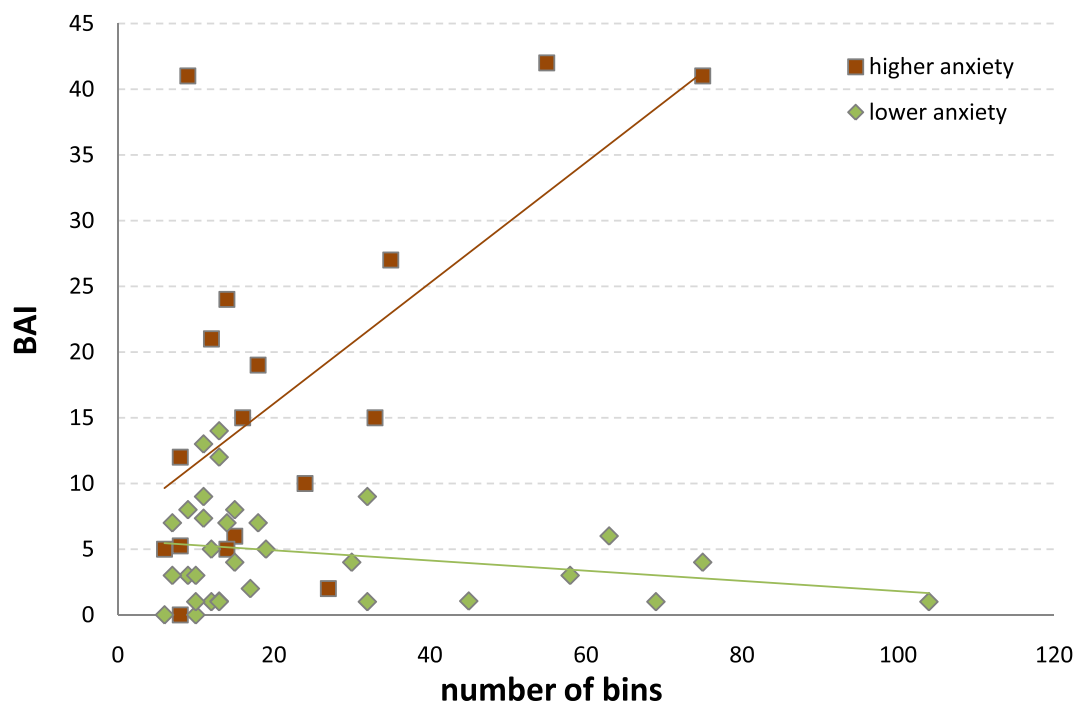
Figure 1. Association of respiration pattern variability (number of bins) and anxiety scores pre intervention in lower and higher (n = 17) anxious subgroups of participants with remitted recurrent depression (n = 49); BAI: Beck anxiety inventory; number of bins: number of respiratory frequency bins above 10% threshold of the main respiration rate.

corrected R^2 = .09, $F_{(4,20)}$ = 0.53, p = .716), at which all predictors were non-significant including both RPV predictors which seemed to play a role in the model (PD CV: B = 10.92, SE = 5.95, β = .43, p = .083; number of bins: B = -0.12, SE = 0.06, β = -.42, p = .059; see supplement for more details).

The pattern of results was the same when excluding all 8 participants who took psychotropic medication.

4. Discussion

We found that MBAT, which included mindfulness-based breathing exercise, had a positive effect on RPV during a sad mood challenge. Therefore, the results suggest that RPV can be influenced by training, which may indicate an underlying biological pathway of interventions using breathing techniques. Further, RPV was associated with anxiety levels at baseline especially in high anxious individuals. Additionally, in the MBAT group RPV changes seemed to be predictive for the outcome regarding anxiety symptoms. These results provide additional evidence for the role of both anxiety and respiration, as well as their interrelation in depression. As intended, the sad mood challenge was perceived as a stressful experience. Additionally, few participants reported low-level stress due to the MRI setting in the beginning during the anatomical scans which subsided until the experiment started. Previous studies have reported stress reduction through altered breathing, e.g. through diaphragmatic breathing (Hopper et al., 2019). Likewise, anxious people can benefit from special breathing techniques (Wannemueller et al., 2016; Yamada et al., 2017). Thus, further supported by our results, a respiration focused intervention might also be useful for individuals with depression, in particular for those with comorbid anxiety symptoms or disorders. One possible mechanism which might also explain our findings, is that slow deep breathing and cardiorespiratory synchronization may have an effect on the amygdala, causing physiologic inhibition of negative emotions (Jerath et al., 2015).

Our analyses focused on the DMN, as we previously found a relation of respiration and DMN connectivity in depression (Zamoscik et al., 2018). The current results however, do not point to any intervention related changes in PCC – parahippocampal and DMN connectivity. As both trainings were brief (about 13h of training overall) and MBAT was not focused on respiration only, we assume that a longer and more intense respiration focused training might cause stronger effects. Trainings using higher intensity, including yoga practices which contain breathing exercises, often lead to a better outcome (Papp et al., 2019). This is also in line with fMRI findings as e.g.Taylor et al. (2013) found neural effects in healthy individuals with 1000h of meditation experience. Therefore, one could expect changes in brain connectivity with increased training duration or intensity. Importantly, most of our participants had a long lasting history of depression, having experienced on average 4–5 major depressive episodes, and were therefore highly vulnerable. These highly vulnerable individuals might present with an imaginable neural scar, typified by increased PCC – parahippocampal connectivity during sad mood, which has been shown to be connected with maladaptive behavior including rumination about negative events (Zamoscik et al., 2014). While changes to this altered connectivity might present a biological target and desired outcome of an intervention, rumination about negative issues is very common in depression. Therefore, interventions might require much more time, especially for recurrent or chronically depressed individuals. Hints that there might be neural correlates of respiration in anxiety were found by another working group during anticipation of anxiety (Masaoka and Homma, 2000). In this study using dipole tracing, the electroencephalograms revealed a wave of positive potentials in limbic areas of the brain about 350ms after the onset of inspiration. This effect illustrates the association of respiration and emotional states, and suggests that respiratory-related neural activities in limbic and paralimbic areas can be observed and seem to correlate with anxiety (Masaoka and Homma, 2000). In future studies, other brain areas should be an additional target of interest when exploring effects of respiration focused trainings.

Of course, there are more aspects influencing RPV and anxiety which occur naturally or through special behaviors we did not assess and could additionally explain variance of the reported effects of MBAT. However, our results during a sad mood challenge point to a significant role of an interplay of respiration and anxiety in depression which can be targeted

with intervention. Accordingly, during rest in remitted depressed individuals we would expect only a slightly altered RPV, which would intensify when confronted with stressful triggers (e.g. negative life events). Acutely depressed participants might show a stronger alteration of RPV already during rest. However, learning new breathing techniques in the scope of an intervention can be challenging enough, so these techniques should first be learned in non-stressful situations. Once mastered, they can be transferred also to stressful situations. To make those interventions as good as possible, respiration related variables should find more attention in future studies to ameliorate personalized interventions, as comorbid anxiety in depression is associated with a worse course of the disorder (Hung et al., 2019). Importantly, PD CV and number of bins during sad mood induction seemed to be differentially associated with BAI scores, pointing to the importance of disentangling various respiration parameters and patterns in relation to their impact on anxiety in future studies. In addition, sex-dependent effects on RPV changes suggest that sex might be a contributing factor in explaining the effect of body-focused interventions on emotions. Therefore, it would also be important in future studies to have a closer look if various sexes profit differently from diverse breathing techniques. As a shortcoming, there were differences between groups in PD CV before training (higher in MBAT group), so the MBAT group could possibly also benefit more than the PMR group as the range for change was larger. When accounting for the baseline values, a medium effect was still there although it was not significant (.058). Based on this observation that the effect is also present when correcting for baseline differences, we conclude that our results would hold true within independent larger samples. Importantly, psychotropic medication did not influence the pattern of results.

Even though our findings need to be replicated in larger studies, our results hint to a beneficial effect of respiration focused interventions for individuals with depression and anxiety. While one can think of vital clinical implications of this study, at the time being, we want to focus more generally on the importance to integrate respiration in interventions for mental health. Additionally, sex, stress, and the type of breathing techniques might have an impact on outcome which has to be further evaluated. This is also highly relevant in regard to relapse risk, as we found recovery/normalization of RPV being also associated with lower relapse risk in formerly depressed individuals (Zamoscik et al., 2018).

Declarations

Author contribution statement

V. Zamoscik: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

C. Kuehner: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

P. Kirsch: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Analyzed and interpreted the data.

C. Timm: Performed the experiments; Contributed reagents, materials, analysis tools or data.

S. N. L. Schmidt: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Competing interest statement

The authors declare no conflict of interest.

Additional information

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