RESEARCH ARTICLE

Interplay of physical and recognition performance using hierarchical continuous-time dynamic modeling and a dual-task training regime in Alzheimer's patients

Svenja Schwarck[1,2] | Manuel C. Voelkle[3] | Andreas Becke[1,2] | Nancy Busse[1,2] | Wenzel Glanz[1,2] | Emrah Düzel[1,2] | Gabriel Ziegler[1,2]

[1]Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke-University, Magdeburg, Saxony-Anhalt, Germany

[2]German Center of Neurodegenerative Diseases (DZNE), Magdeburg, Saxony-Anhalt, Germany

[3]Institute of Psychology, Humboldt University of Berlin, Berlin, Germany

Correspondence
Svenja Schwarck, Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke-University Magdeburg ,Leipziger Str. 44, 39120 Magdeburg, Germany.
Email: svenja.schwarck@med.ovgu.de

Emrah Düzel and Gabriel Ziegler shared senior authorship.

Abstract

Training studies typically investigate the cumulative rather than the analytically challenging immediate effect of exercise on cognitive outcomes. We investigated the dynamic interplay between single-session exercise intensity and time-locked recognition speed-accuracy scores in older adults with Alzheimer's dementia ($N = 17$) undergoing a 24-week dual-task regime. We specified a state-of-the-art hierarchical Bayesian continuous-time dynamic model with fully connected state variables to analyze the bi-directional effects between physical and recognition scores over time. Higher physical performance was dynamically linked to improved recognition (-1.335, SD = 0.201, 95% Bayesian credible interval [BCI] [-1.725, -0.954]). The effect was short-term, lasting up to 5 days (-0.368, SD = 0.05, 95% BCI [-0.479, -0.266]). Clinical scores supported the validity of the model and observed temporal dynamics. Higher physical performance predicted improved recognition speed accuracy in a day-by-day manner, providing a proof-of-concept for the feasibility of linking exercise training and recognition in patients with Alzheimer's dementia.

KEYWORDS
Alzheimer's disease, Bayesian, cardiovascular training, cognitive performance, continuous-time modeling, dynamic modeling, hierarchical, intervention, longitudinal analysis

Highlights

- Hierarchical Bayesian continuous-time dynamic modeling approach
- A total of 72 repeated physical exercise (PP) and integrated recognition speed-accuracy (IRSA) measurements
- PP is dynamically linked to session-to-session variability of IRSA
- Higher PP improved IRSA in subsequent sessions in subjects with Alzheimer's dementia
- Short-term effect: lasting up to 4 days after training session

1 | BACKGROUND

Alzheimer's disease (AD) involves neuropathological changes including accumulation of amyloid plaques, neurofibrillary tangles, and neuronal and synaptic loss resulting in macrostructural atrophy of the brain.[1] AD causes a progressive decline in functional independence, particularly affecting episodic memory early on.[1,2] Regular physical activity (for definition see Supplemental Material) seems to reduce AD risk substantially[3] by reducing $A\beta$ plaques, increasing hippocampal plasticity/neurogenesis, and improving memory.[4–7] Acute exercise already has small effects on episodic memory,[8,9] whereas training seems to enhance hippocampal structure and function, episodic memory (g = 0.28), such as recognition performance, but also processing speed (g = 0.158) and executive functions (g = 0.123).[4,7,10–12]

Therefore, targeted interventions focusing on physical inactivity are under investigation to delay the progression of memory decline.[13] Several intervention studies reported positive effects of aerobic exercise training on physical fitness and episodic memory performance in patients with AD or mild cognitive impairment,[14] while others observed no effects despite physical improvements.[15,16] This inconsistency may arise from differences in training methodology. While moderate-intensity exercise training for at least 24 weeks (three sessions and 40 minutes/week) seems to most strongly enhance episodic memory performance, studies vary in parameters like intensity and length.[14,17]

Exercise interventions in dementia are typically envisioned as prolonged regimes of regular weekly training sessions spanning several months. During this time, the exercise intensity is gradually increased according to individual parameters (eg, heart rate, resistance). Given the prolonged nature of exercise interventions, it is clinically relevant to understand how each training session and changing parameters affect cognition, both during training and shortly after training. These time-locked, immediate effects of training, examinable via dual-task regimes, are important for several reasons. First, they can provide mechanistic insights into the training-related day-to-day fluctuations of cognition of a patient to develop more effective approaches and guide care and clinical decision-making. Second, they can provide individual guidance for adaptively choosing the optimal training intensity from a cognitive point of view.

To summarize, there is partial support for the hypothesis that regular physical activity might positively impact cognition.[3,18] However, longitudinal modeling approaches often present unclear directions or mean trajectories rather than analyzing their dynamic changes and interplay (CR, cross-effects) during the course of training.[19,20] Temporal precedence, that is, prediction of values of a variable from previous values of another variable, is vital for causality.[21] Moreover, time is often treated as a discrete variable and accordingly, the regression strength between time points is estimated without integrating information regarding the interval between them.[21,22] Previous longitudinal studies therefore faced challenging unequal time interval lengths between and/or within participants, which might lead to biased parameter estimates and conclusions.[21–23] In contrast, a hierarchical Bayesian continuous-time dynamic modeling approach overcomes problems of conventional approaches, such as the above biases and lack of temporal precedence.[19,20] This approach enables the analysis of the dynamic change and mechanistic coupling between states of interest, fully accounting for unequal acquisition time intervals.[21,24]

Here we study the dynamic changes of physical and recognition performance and their interplay using an extensive longitudinal training study for patients with suspected AD comprised of 72 sessions over 24 weeks, including a physical and recognition dual-task regime. The positive exercise-induced effect of physical fitness on recognition was shown in a previous paper using a conventional linear approach.[25] In this study, we focus on the dynamic interplay between physical and recognition performance taking advantage of state-of-the-art hierarchical Bayesian continuous-time dynamical system modeling.[21,24,26] We hypothesize that changes in physical performance predict subsequent changes in recognition performance. In addition, we hypothesize that individual dynamics relate to dementia symptom severity as well as physical health.

2 | METHODS

2.1 | Sample and experimental design

We recruited older adults aged 60 to 80 years with diagnosed mild to moderate AD (International Classification of Diseases, Tenth Revision [ICD-10], classification F00.1; Mini-Mental State Examination [MMSE]: 18 to 26) from the memory clinic of the German Center for Neurodegenerative Diseases (DZNE), Magdeburg (see the Supplemental Material: Methods in supporting information). The total sample size included $N = 17$ older adults (age: $M = 73.33 \pm 3.43$ years; MMSE: $M = 23.50 \pm 3.45$; female = 8) who were free of depressive symptoms (Geriatric Depression Scale: $M = 1.88 \pm 0.93$), and pulmonary and cardiovascular diseases.

The study contained a 24-week (72 sessions, 15-minutes each) dual-task regime (for details see also[25]) with pre-and post-assessment by the MMSE and the 12-Item Short Form Survey (SF-12) physical health questionnaire.[27] Subjects cycled on a stationary bike (40 to 80 rotations per minute), with intensity increasing every 60 seconds after reaching the target heart rate (HR) (65% to 75% of maximum HR calculated via the Karvonen method: $220 - age$[28]), while also memorizing 30 pictures. Recognition performance (forced-choice task) was assessed immediately after training with 30 subsequent screens showing two pictures, the original and a lure picture, each.

2.2 | Physical and recognition performance measures

We included up to 72 training sessions per participant in the analysis if completed (90% of the sample). The training observations were z-standardized (grand mean centering and scaling) on the global level. Physical performance (PP) was measured as the ratio of power output (unit: Watt; measure of exercise intensity) and HR of each

RESEARCH IN CONTEXT

1. **Systematic review**: Training-induced effects on cognitive outcomes in Alzheimer's dementia and/or associated dynamic Bayesian modelling approaches were reviewed. Although studies showed exercise-induced cognitive improvements or maintenance, most of these studies fail to capture the dynamic nature of the change and interplay of physical (PP) and integrated recognition speed-accuracy (IRSA) performance.

2. **Interpretation**: Using a sophisticated hierarchical Bayesian continuous-time dynamic modelling approach, a fully connected state variable model was specified. PP is dynamically linked to IRSA, i.e. higher PP predicted improved COG in subsequent sessions. This effect was rather short term, lasting for up to four days.

3. **Future direction**: Our results support exercise-induced effects on cognition. The cognitive system was still able to fluctuate and change favourably even in a sample with Alzheimer's dementia. Further studies using dynamic modelling are necessary to replicate findings and examine other contributors to cognitive volatility in dementia.

training session. Higher values reflect higher PP. Integrated recognition speed-accuracy (IRSA) as recognition performance (episodic memory) outcome was operationalized as reaction times (RTs) corrected for the number of errors. The RT (in seconds) within a valid range of ≤ 13 seconds (average per session) was used and corrected for the proportion of error (PE) using the linear integrated speed-accuracy score (LISAS)[29]:

$$\mathbf{LISAS}\,(j) = \mathrm{RT}\,(j) + \frac{\mathrm{SD_{RT}}}{\mathrm{SD_{PE}}} * \mathrm{PE}\,(j), \qquad (1)$$

with mean RT and proportion of errors at the measurement occasion j, and respective standard deviations. Lower scores reflect higher IRSA.

2.3 | Dynamical Bayesian modeling and statistical analysis

All statistical analyses were conducted in R version 4.0.2 using RStudio version 1.3.1056. The modeling approach was previously established and implemented in the R package ctsem[26] relying on Stan software.[30] Results were visualized using ctsem and ggplot2 from tidyverse.[31] Model fit was compared using chi-square tests. The alpha level for additional frequentist statistical tests was defined as $p < 0.05$.

Hierarchical Bayesian continuous-time dynamic modeling was used to simultaneously analyze the temporal dynamics of PP and IRSA reflected in a 2-dimensional state variable $\eta(t) = [\mathrm{PP}(t), \mathrm{IRSA}(t)]^{\mathsf{T}}$ at time t.[26] At the core is a subject-level latent dynamic model using a

stochastic differential equation (or state equation):

$$d\boldsymbol{\eta}\,(t) = \left(\mathbf{A}\boldsymbol{\eta}\,(t) + \mathbf{b} + \mathbf{M}\boldsymbol{\chi}\,(t)\right)\,dt + \mathbf{G}d\mathbf{W}\,(t), \qquad (2)$$

with time-varying latent process $\eta(t)$ and its temporal derivative $d\eta(t)$ encoding the system's current state and its change over time, respectively. The DRIFT-matrix **A** contains free parameters and defines the temporal dynamics of the process with auto-effects (self-connections: main-diagonal) and cross-effects (coupling: off-diagonal). Equation (2) contains the continuous-time intercept (CINT) **b**, the effect **M** of time-dependent predictors χ on $\eta(t)$, and $d\mathbf{W}(t)$, the stochastic noise term (random fluctuations) with **G** capturing the effect of the these on the process (DIFFUSION).

The continuous-time parameters of **A** contain changes of η over a small time interval in the differential equation and can be transformed into better interpretable discrete-time equivalents (**A***) for any given time interval length (Δt):

$$\mathbf{A}^{*}_{\Delta t_u} = e^{\mathbf{A}(t_u - t_{u-1})}, \qquad (3)$$

where $\mathbf{A}^{*}_{\Delta t_u}$ includes the associated auto- and cross-regression effect for the effect of η at the measurement occasion u-1 on η at measurement occasion u.[26] The approach utilized also includes a linear measurement model relating latent states $\eta(t)$ to observables $\mathbf{y}(t)$:

$$\mathbf{y}\,(t) = \mathbf{\Lambda}\boldsymbol{\eta}\,(t) + \tau + \varepsilon\,(t), \qquad (4)$$

using factor loadings $\mathbf{\Lambda}$, the manifest intercepts τ and residuals ε with covariance matrix $\mathbf{\Theta}$ (see Supplemental Material).

The dynamic model was specified with two fully connected state variables enabling bi-directional coupling between PP and IRSA over 72 measurement occasions. The observable indicator Power/HR of each session were loading on PP and LISAS on IRSA. All other parameters (except **b** and **M,** which were set to zero) of the state equation and measurement model were left free to be estimated using the data. The latent process means at $t = 0$, τ (intercepts) and **A** (DRIFT-matrix) were allowed to vary freely across participants, resulting in 49 parameters. Population and individual-level parameters are estimated simultaneously using all data from all subjects. The hierarchical Bayesian model estimation was set to default priors and initial starting values using four chains and 8000 iterations (under Stan's optimizer for maximum a posteriori estimates).

Four models were hypothesized and further compared: a full 2-CR model (both auto- and cross-effects, 13 free population mean parameters), two 1-CR models with unidirectional interactions PP→ISRA (CR of interest) and ISRA→PP (without CR of interest) and a zero-model (0-CR) with auto-effects only. The full 2-CR model was compared against both the 1-CR and 0-CR models with regard to their model fit using a chi-square difference test.[26]

Furthermore, we ran a second-level model with the MMSE and the SF12 baseline scores as time-independent covariates for validation with the temporal dynamics. A higher score in both covariates is associated with higher cognitive and physical health status respectively.

TABLE 1 Demographic data.

Demographic data	
Age (years)	67–80 (M = 73.41, SD = 3.43)
Sex	7:10 (ratio female to male)
Neurological characteristics	
ICD-10 diagnosis	Alzheimer's disease (F00.1)
MMSE pre	M = 23.35, SD = 3.50
MMSE post*	M = 22.75, SD = 4.06

Notes: Demographic data and neurological characteristics of the sample (N = 17). ICD-10, International Classification of Diseases, Tenth Revision; MMSE pre, Mini-Mental State Examination score before the start of the intervention. MMSE post, Mini-Mental State Examination score after the end of the 24-week intervention (assessment within 12 days to 8 weeks after the intervention).
*N = 16 due to one missing post-assessment. M, mean. SD, standard deviation.

All other model specifications were the same as the above full 2-CR model.

To explore potential changes in the domain interplay over the course of the training, the strength of PP on IRSA (PP→IRSA) was compared between the baseline (days 1 to 84) and second half (days 85 to 168) of the training (both free parameters to estimate). By specifying a slightly extended full 2-CR model, we included a time-dependent predictor χ (named "secondhalf"), which is zero except on day 84, when it is 1. Additionally, an extra latent process (named "step2ndhalf") was included, with all parameters and covariances fixed to zero, except the element on the time-dependent predictor was set to 1 (step function), that is, the extra latent process shifts on day 84 to 1 and stays there. The cross-effect in question was defined as a function of PP→IRSA on baseline added by PP→IRSA on the second half of the training multiplied by the extra latent process. A negative value reflects a stronger effect of PP→IRSA (ie, when PP increases the RT decreases) in the second half of the training and vice versa. The model was compared with a model for which $\chi = 0$ using a nested chi-square difference test.

3 | RESULTS

3.1 | Demographic data

Table 1 provides the demographic data and associated neurological characteristics of the participants.

3.2 | Analysis of cross-domain interplay using dynamic modeling

The range of valid measurement occasions of all 17 participants was between 59 and 70 sessions (M = 64.71 ± 4.26) resulting in 1100 manifest observations per latent state (or domain) with 25 (≈2.3%) missing values for PP. The time interval between successive measure-

ment occasions ranged from 1 to 14 days (M = 2.54 ± 1.04). The longitudinal data were analyzed using a two-state dynamical model as illustrated in Figure 1 (for details see Methods).

A chi-square difference test for model comparison revealed a significant difference between the full 2-CR model and the 0-CR model, $\chi^2(17) = 235.1$, $p < 0.001$. In addition, a significant difference was also observed between the 2-CR model and the PP→IRSA 1-CR model, $\chi^2(9) = 149.8$, $p < 0.001$, and the IRSA→PP 1-CR model, $\chi^2(9) = 194.6$, $p < 0.001$. Correspondingly, the full 2-CR model (Table 2) containing both cross-effects that enable a bi-directional interplay between IRSA and PP fitted the data best and is further reported (see Table S1 for estimated population parameters for the other models).

Changes in PP predict later changes in IRSA in the opposite direction as found by a more substantial negative cross-effect drift$_{PP→IRSA}$ (−1.335, SD = 0.201, 95% Bayesian credible interval [BCI] [−1.725, −0.954]). As such, when physical performance levels are above baseline (suggesting higher PP) IRSA levels are likely to go downwards. The cross-effect PP→IRSA also varies between participants, which suggests that some subjects benefit more from the exercise training resulting in recognition improvements than others (between-person variability in drift$_{PP→IRSA}$: 2.44, SD = 0.29, 95% BCI [1.86, 3.02]). In contrast, IRSA values do partially predict later changes of PP in the same direction as indicated by a small and positive cross-effect (drift$_{IRSA→PP}$). When a subject's RT increases (ie, reduced IRSA) the PP levels did also slightly increase over the ensuing time. Furthermore, the temporal changes of PP last longer than the temporal dynamic of IRSA (higher auto-effect of PP [drift$_{PP}$]).

Previous states of PP do impact IRSA negatively (−0.368, SD = 0.05, 95% BCI [−0.479, −0.266]) as shown via discrete-time parameters (1-day time interval). The expected effect PP→IRSA peaks around 1 and lasts for up to around 4 days, after which the random-state fluctuations dominate (Figure 2). The cross-lagged effect IRSA→PP was observed to be close to zero (0.086, SD = 0.024, 95% BCI [0.041, 0.136]) and accordingly there is practically no substantial effect in this direction. Furthermore, the small autoregressive (self-connection) effect of IRSA (0.145, SD = 0.039, 95% BCI [0.072, 0.226]) suggested low stability of the construct over time. PP on one day had a small effect on PP on another day (0.363, SD = 0.05, 95% BCI [0.264, 0.472]).

The temporal dynamics of PP showed more inter-individual differences compared to IRSA. Some subjects showed relatively persistent PP levels over the entire training time, while the PP fluctuated more in other participants (between-person variability in drift$_{PP}$: 9.89, SD = 0.52, 95% BCI [8.89, 10.90]). The measurement error (MANIFEST$_{VAR}$) of the manifest indicator Power/HR (0.208) was found to be higher compared to LISAS (0.046); that is, measurement limitations and short-term situational influences (eg, subjective stress or sunny days) are more present in the PP indicator (Table 2), and IRSA showed higher session-to-session fluctuations within-person (0.188, SD = 0.014, 95% BCI [0.163, 0.217]) compared to PP (0.004, SD = 0.002, 95% BCI [0.001, 0.012]). The model prediction of IRSA and PP over training time is illustrated in Figure 3 (see also Supplemental Material Figure S1 for five randomly selected participants).
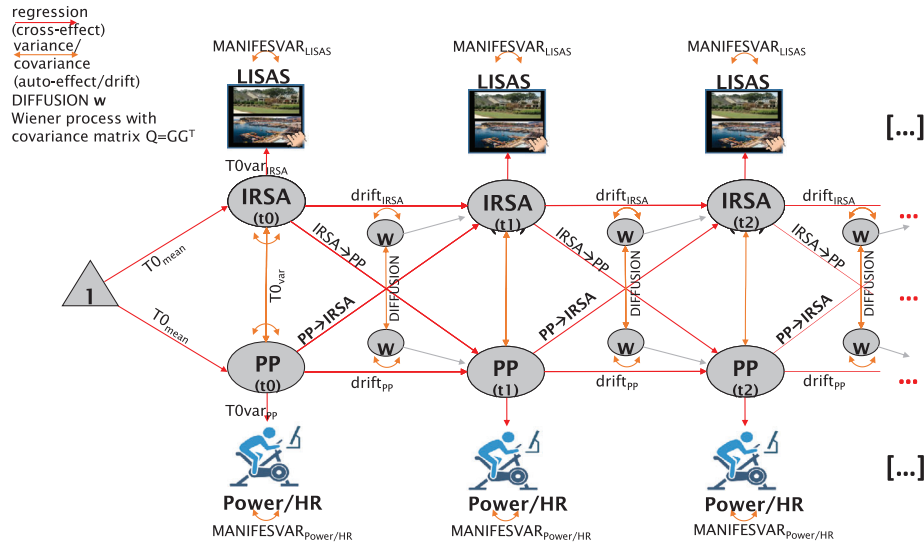
FIGURE 1 Schematic illustration of the two-state model with the first three timepoints (t0, t1, t2) reflecting successive training sessions. The graphical model contains the observed variables (manifest indicators [MANIFESVAR]), power of the bicycle ergometer and heart rate (HR; as the ratio: Power/HR) and reaction time corrected for the proportion of error (linear integrated speed-accuracy score [LISAS]), loading on the latent variables (ellipsoids) of physical performance (PP) and integrated recognition speed-accuracy performance (IRSA), respectively. The main effect of interest is the cross-effect of PP on IRSA (further denoted as cross-effect drift$_{PP\to IRSA}$). The model also contains latent error terms (**w**) and the continuous-time intercept (triangle). The model shows regression paths (red lines) and variance and covariance (orange lines). Manifest intercepts are not shown.

TABLE 2 Group level results, full 2-CR model.

| Parameter	Symbol	*Est.*	*SD*	*LL-BCI*	*UL-BCI*
DRIFT					
drift$_{PP}$	A	−0.851	0.146	−1.146	−0.602
drift$_{IRSA}$	A	−1.645	0.188	−2.026	−1.300
cross-effect$_{IRSA\to PP}$	A	0.313	0.087	0.154	0.485
cross-effect$_{PP\to IRSA}$	A	−1.335	0.201	−1.725	−0.954
T0$_{MEANS}$					
T0m$_{PP}$	η_1	−0.175	0.010	−0.194	−0.154
T0m$_{IRSA}$	η_2	0.941	0.083	0.766	1.102
DIFFUSION					
diff$_{PP}$	Q	0.045	0.011	0.027	0.070
diff$_{IRSA}$	Q	0.797	0.038	0.722	0.874
diff$_{PP\_IRSA}$	Q	−0.687	0.135	−0.884	−0.354
MANIFEST$_{VAR}$					
mvar$_{Power/HR}$	Θ	0.208	0.006	0.195	0.220
mvar$_{LISAS}$	Θ	0.046	0.029	0.012	0.124
MANIFEST$_{MEANS}$					
mm$_{Power/HR}$	τ	−0.382	0.078	−0.531	−0.234
mm$_{LISAS}$	τ	0.259	0.079	0.103	0.412

Note: Group-level results showing estimated population means including Bayesian posterior intervals of the full 2-CR (cross-effect) model. Sample size *n* = 17 with 1100 observed sessions in total. The model contains two latent variables (physical performance [PP] and integrated recognition speed-accuracy [IRSA] performance) with one manifest indicator, each (Power/HR and LISAS) respectively; *n* = 13 free population mean parameters; Bayesian model estimation: number of chains = 4, number of iterations = 8000. Est., mean from mean of the chains; BCI, 95% Bayesian credible interval; LL, lower limit; UL, upper limit.

### 3.3 | Drift coefficients as a function of clinical baseline scores

Participants with higher MMSE baseline scores show lower persistence in the cross-effect IRSA→PP (drift$_{IRSA\to PP}$; −0.215, SD = 0.022, 95% BCI [−0.259, −0.172], Figure 4A). Higher MMSE baseline scores were associated with lower persistence in IRSA (drift$_{IRSA}$; −0.538, SD = 0.174, 95% BCI [−0.887, −0.209]). The effect of MMSE on the auto-effect PP and the cross-effect PP→IRSA is close to zero (−0.02, SD = 0.003, 95% BCI [−0.03, −0.01]). Participants with a lower health score show a stronger cross-effect of IRSA on PP (drift$_{IRSA\to PP}$; −0.231, SD = 0.035, 95% BCI [−0.303, −0.165], Figure 4B). Likewise, higher physical health scores seem to be associated with lower persistence in their PP (drift$_{PP}$; −0.036, SD = 0.008, 95% BCI [−0.052, −0.021]). The effects on the other auto-effect and cross-effect are close to zero.

### 3.4 | Changes of dynamics over the course of training

An extended model with the drift coefficient PP→IRSA as a function of time was specified. The model estimated if the strength of the cross-effect PP→IRSA changed between the baseline (days 1 to 84) and the second half (days 85 to 168) of training. Results suggested that the cross-effect PP→IRSA becomes positive in the second half of the training (2.08); that is, the strength and associated effect of PP on recognition performance was found to be reduced in the second half of training. This change was estimated as a function of PP→IRSA on baseline (−0.11, SD = 0.63, 95% BCI [−1.34, 1.14]) added to PP→IRSA on the second half of the training (−1.50, SD = 0.08, 95% BCI [−1.66,
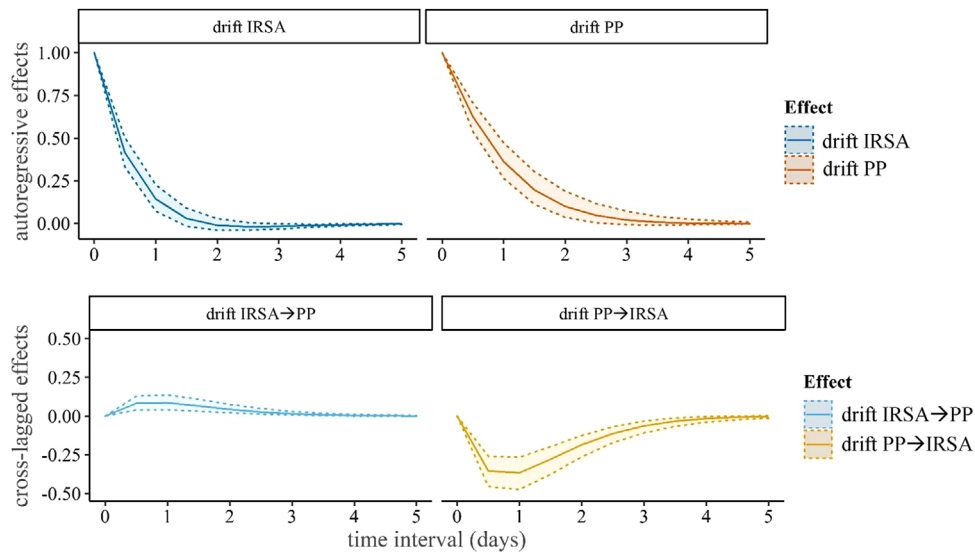
FIGURE 2 Auto- and cross-regression over time. Temporal autoregressive effects (upper panel) and cross-lagged effects (lower panel) over time (x-axis, time interval in days), median and 95% quantiles for a change of 1 at time zero. The expected autoregressive effect (or self-connection) of physical performance (PP; drift PP) and integrated recognition speed-accuracy (IRSA; drift IRSA) peak around approximately 1 day and decrease with increasing time interval length. This suggests that the more time passes the less predictive is the performance for consecutive performance levels. The expected cross-lagged effect (or interplay) of PP on IRSA peaks around 1 day and seem to improve predictions of IRSA for up to around 4 days. This can be understood as rather short-term benefits from physical training on cognitive performance. The cross-lagged effect of IRSA on PP is very close to zero, suggesting that changes in cognitive performance do not improve predictions of physical performance.
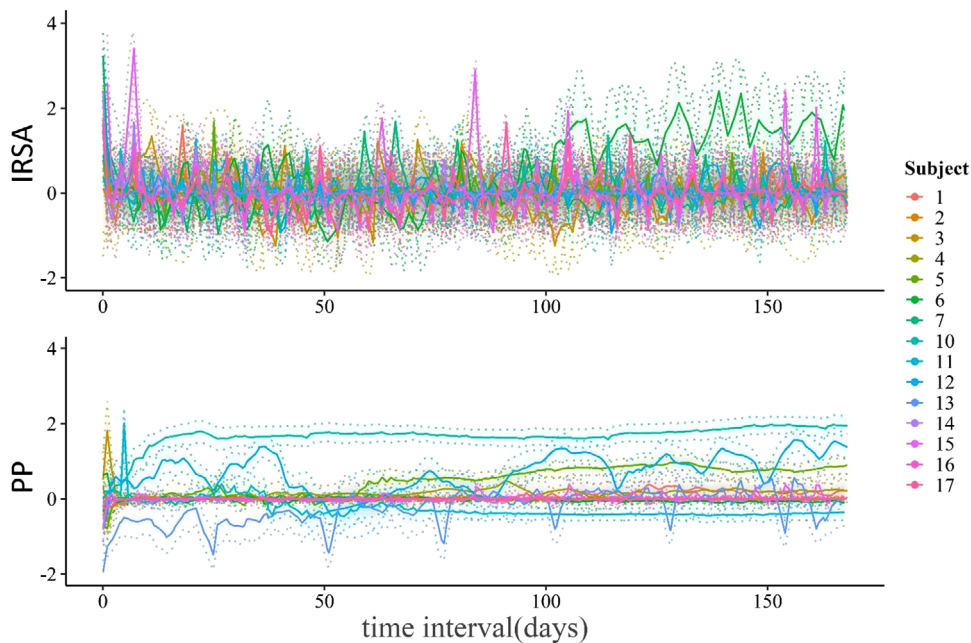
FIGURE 3 Individual estimates of integrated recognition speed-accuracy (IRSA) and physical performance (PP), showing individual-level analyses for all participants of the sample ($n = 17$) over the time interval in days (x-axis). The solid lines present the model prediction of the smoothed estimates of participant's individual latent states IRSA (upper panel) and PP (lower panel) within a 95% Bayesian credible interval (BCI). Each colored solid line presents the individual model prediction for one subject. The temporal dynamics of PP show more individual differences compared to IRSA.
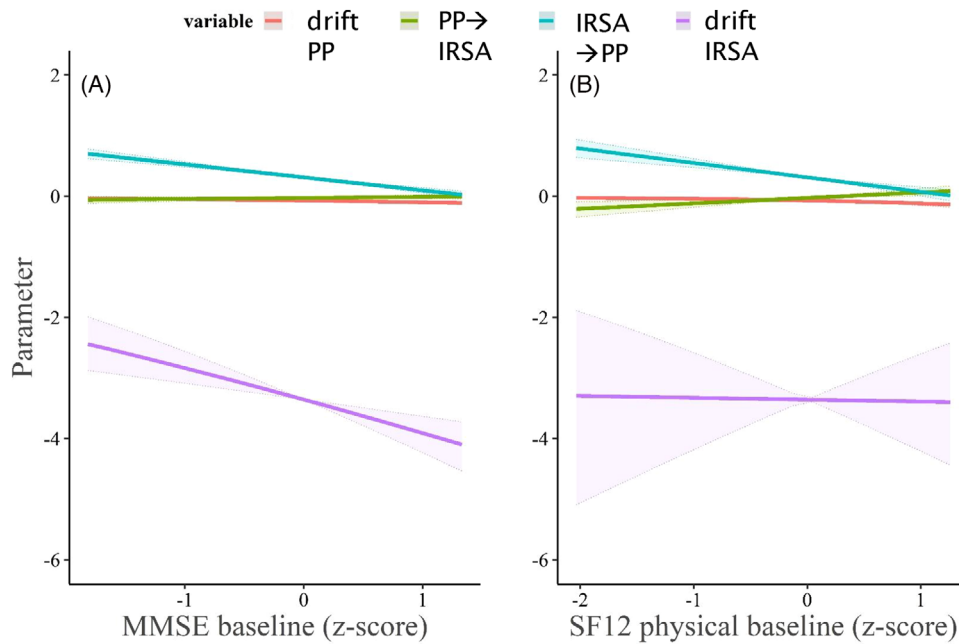
FIGURE 4 Estimated effect of subject-level covariate predictors on dynamic parameters. We show (A) MMSE and (B) SF12 physical health baseline score effects on drift parameters (auto-effects and cross-effects) within a 95% Bayesian credible interval (BCI). drift_{PP}, auto-effect PP (red solid line); $\text{drift}_{PP \to IRSA}$, cross-effect PP on IRSA (green solid line); $\text{drift}_{IRSA \to PP}$, cross-effect IRSA on PP (blue solid line); drift_{IRSA}, auto-effect IRSA (purple solid line); IRSA, integrated recognition speed-accuracy; MMSE, Mini-Mental State Examination; PP, physical performance; SF12, 12-Item Short Form Survey.

−1.34]) multiplied by the extra latent step process (−1.45, SD = 0.38, 95% BCI [−2.21, −0.72]). The chi-square difference test for model comparison revealed a significant difference between the extended model and a model for which the time-dependent predictor is zero, $\chi^2(1) = 464.85$, $p < 0.001$.

4 | DISCUSSION

Recent longitudinal studies reported mixed effects of exercise training on episodic memory performance in dementia patients,[14] often failing to capture the dynamic coupling between PP and IRSA.[21] This study utilized Bayesian hierarchical continuous-time dynamic modeling[26] to assess session-to-session changes and interplay of PP and IRSA over 72 measurements.

Under the assumption of our model, PP is dynamically linked to IRSA, which combines LISAS to access recognition performance and processing speed. This addresses conflicts such as slower responses in elderly participants, error-prone processes in speeded forced choice and the nonlinear speed-accuracy trade-off.[29,32–34] Thus, increased PP was associated with improved IRSA, which is in line with previous training studies.[3,18] However, this effect shows between-person variability, suggesting that some participants benefited more from the training than others. While we cannot rule out the possibility of nonresponders due to a missing control group,[35] the observed cross-effect supports the notion that exercise training has a positive effect on IRSA in dementia. Diagnostic tools like HR variability[36] enable precise adjustments (eg, intensity, duration), preventing physical strain or underload to optimize immediate effects on IRSA.

In addition, an important question is how long this beneficial exercise-induced effect on IRSA lasts (eg, how many days). Our results suggest a rather short-term effect: A positive change in PP can improve the prediction of increased IRSA for up to 4 days with the strongest influence after 1 day, after which unpredictable random fluctuations dominate. However, unexplained or not modeled causes could act on this effect and might appear even without training. Nevertheless, the coupling-effect appears at least under the condition of training, consistent with recent studies.[3,18] Given the high cost of dementia care and drug treatment side effects,[37,38] our non-pharmacological approach may provide a cost-effective alternative to enhance episodic memory in AD patients.

Furthermore, we observed random session-to-session cognitive fluctuations within participants over time, while the measurement error was close to zero. In patients with AD, intra-individual cognitive fluctuations are generally higher compared to healthy controls[39] and may be linked to pathology.[40] Considering this fluctuation as measurement error only would oversimplify the true cognitive state.[41] Thus, studies may examine the question of how cognitive fluctuations can be used since they are random.

In line with recent studies,[7,11,12,14] we observed exercise-induced effects on IRSA. Using dynamic Bayesian modeling, we demonstrated that PP is dynamically linked to IRSA, with short-term effects suggesting that exercise mobilizes dormant capacities. However, the exercise-induced causal underlying mechanism(s) are still being discussed.[42,43] Evidence suggests neurotrophin-mediated neurogenesis, like brain-derived neurotrophic factor (BDNF).[44] Inhibiting hippocampal BDNF, by blocking tyrosine receptor kinase B, also inhibited its beneficial effects on episodic memory.[45] The short-term nature of the effect that

we report here suggests that rather than the chronic and slow plasticity related to neurogenesis, more immediate mechanisms may play a role, such as changes in the bodily milieu, improved perfusion, and improved clearance.[44,46,47]

We further assessed the drift coefficients as a function of clinical baseline scores. Higher physical health (SF-12) and lower cognitive impairment (MMSE) were associated with lower persistence, that is, less stability, in PP and IRSA, respectively (the higher the clinical score, the smaller the corresponding auto-effect, ceteris paribus). This suggests that each baseline score corresponds to its respective latent state, providing further support for the observed temporal dynamics.

PP showed a general increasing trend and IRSA a decreasing trend over training time, consistent with our prior linear-mixed modeling approach.[25] Moreover, we observed changes in the coupling effect of PP on IRSA over training time, particularly evident in the first half (days 1 to 84), aligning with previous training studies.[48] In contrast, this coupling-effect weakened in the second half (days 85 to 168). One explanation might be that the changes may follow a nonlinear time course, for example, by increasing early or close to the end of the whole training regime, warranting further investigations using time-varying analysis. However, patients with AD show general reduced motivational capacities.[49] Animal studies observed positive effects of environmental enrichment (combined physical, cognitive, and social stimulation) on brain health, including increased neurotrophic factor levels, neurogenesis, and improved memory performance.[50] Although our training was designed as a cognitive motivation, that is, the participants had to physically exercise for new pictures to stimulate the novelty-exploration, reduced task variability may have led to reduced motivation and/or increased distraction from the middle of the training onwards.

Finally, we want to mention several limitations of the current study. Although the model is mechanistic (or causal) it contains many assumptions that might be wrong and/or we may have not included all observable factors mediating the observed effects. Our approach assumed stationary dynamics over the course of the training; that is, we cannot rule out non-stationary dynamics during the training time. The sample was small ($N = 17$) and potentially biased regarding age and severity of AD and did not include a control group due to practical reasons, including the challenge of recruiting and maintaining such a cohort, as well as funding. Since there is an absence of a physically inactive control group, future studies might look if cognitive volatility (ie, also short-reaching performance highs) is present without training and whether the coupling of physical on recognition performance still exists without such training. With regard to the present literature showing positive outcomes due to regular exercise,[18] the latter possibility might not be the case. Future longitudinal randomized controlled studies using a more comprehensive neuropsychological assessment to examine transfer effects are necessary to verify our results.

The present extensive 24-week longitudinal training study examined the temporal connectivity und coupling of PP and IRSA in a sample with AD using a hierarchical Bayesian continuous-time dynamic modeling approach. PP was dynamically linked to IRSA, that is, higher PP improved time-locked IRSA in subsequent sessions. The beneficial effect was rather short-term, lasting up to 4 days after the training. Our observed dynamics were validated by clinical scores; that is, higher MMSE baseline scores were associated with lower persistence in the temporal dynamics of IRSA. To summarize, our results provided a proof-of-concept regarding the feasibility of a time-resolved linkage of exercise training and IRSA even in a sample with suspected AD.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All participants and their relatives as representatives signed a written informed consent form for participation, in accordance with the ethical standards set by the Otto-von-Guericke University, Magdeburg, Germany review boards. The study was approved by the ethics committee of the Otto-von-Guericke University, Magdeburg, Germany (approval number: 68/17).

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