Neurobiology of Aging 157 (2026) 36–47

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging.org

Apraxic deficits in Alzheimer's disease are associated with altered dynamic connectivity in praxis-related networks

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ARTICLE INFO

Keywords:
Motor system
Aging
Cologne apraxia screening (KAS)
Functional magnetic resonance imaging
Resting-state
Alzheimer's disease
Praxis

ABSTRACT

Apraxia is a common symptom in Alzheimer's disease (AD) that reduces autonomy and quality of life. However, the neural basis underlying apraxia in AD, for example, reflected by functional connectivity (FC) alterations, remains unexplored. We investigated static and dynamic FC using resting-state functional imaging in 14 patients with biomarker-confirmed AD pathology and 14 matched healthy participants. FC was estimated as average (static) and short-term (dynamic) connectivity strengths between motor- and praxis-related functional networks. Recurring connectivity patterns were clustered into dynamic states to compute temporal connectivity measures. Connectivity measures were used for correlations with apraxic deficits. In AD patients, static connectivity between visual and inferior parietal networks correlated with apraxic imitation ($r = 0.762$, $P_{FDR} = 0.043$) and arm/hand gesture deficits ($r = 0.848$, $P_{FDR} = 0.020$), while dynamic connectivity between these networks correlated with apraxic imitation deficits ($r = 0.851$, $P_{FDR} = 0.020$). Dynamic FC analysis revealed a segregated and integrated state. AD patients spent more time overall (fraction time, $P_{FDR} < 0.001$) and remained longer without switching (dwell time, $P_{FDR} = 0.004$) in the segregated state. Both fraction ($\rho = -0.858$, $P_{FDR} = 0.015$) and dwell time ($\rho = -0.914$, $P_{FDR} = 0.003$) correlated with apraxic imitation deficits. Connectivity strengths between visual and inferior parietal networks and fraction time in the segregated state predicted apraxic imitation deficits (adjusted $R^2 = 0.782$, $P < 0.001$). We conclude that apraxia in AD patients is associated with altered FC in praxis-related networks, suggesting FC as a potential clinical indicator for predicting motor-cognitive deficits.

1. Introduction

Apraxia is a higher-order motor disorder that affects the ability to perform purposeful, goal-directed actions (i.e., gesture imitation, pantomiming the use of objects, and/or actual object use) and which cannot be explained by primary motor or sensory deficits, comprehension problems, or spatial disorientation (Cubelli, 2017; Osiurak and Rossetti, 2017). Apraxic deficits pose significant challenges in the daily lives of affected individuals. For instance, impairments in gesture production can compromise communication, particularly in aphasia (Borod et al., 1989; Feyereisen et al., 1988). Several studies have linked apraxia severity to reduced independence in activities of daily living, such as dressing and brushing teeth (Goldenberg and Hagmann, 1998), as well as bathing, toileting, grooming, and eating (Hanna–Pladdy et al., 2003). Thus, apraxic deficits contribute to a decreased quality of life and a loss of autonomy.

Apraxia is assumed to result from damage to praxis networks, comprising cortical areas and their connections, needed for planning

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https://doi.org/10.1016/j.neurobiolaging.2025.09.007
Received 6 December 2024; Received in revised form 15 September 2025; Accepted 17 September 2025
Available online 18 September 2025

and executing movements and located in the frontal, temporal, and parietal lobes of the motor dominant hemisphere (Schmidt et al., 2022). Apraxia occurs in a variety of neuropsychiatric diseases such as stroke, schizophrenia, Parkinson's disease, or Alzheimer's disease (AD; Schmidt and Weiss, 2022a). In AD, apraxic symptoms are observed in around 30–90 % of individuals (Lesourd et al., 2013; Stamenova et al., 2014) and commonly manifest as limb apraxia, with a particular impairment in the imitation of finger and hand gestures (Johnen et al., 2015). In stroke patients, apraxic imitation deficits are associated with lesions to the motor-dominant inferior parietal lobe (IPL; Schmidt and Weiss, 2022b) and intraparietal sulcus (IPS; Hoeren et al., 2014). These regions receive input from visual areas as part of the dorsal processing stream (Binkofski and Buxbaum, 2013). Despite the substantial limitations that apraxia imposes on daily activities (Dovern et al., 2012), research on apraxia in individuals with AD remains scarce. While it is known that apraxic imitation deficits occur early in AD and are associated with structural atrophy (Johnen et al., 2016) and specific tau depositions (Bischof et al., 2024), the functional mechanisms underlying apraxia in AD remain elusive. Since stroke-related apraxia is assumed to be associated with disrupted activation and connectivity between higher-order motor areas (Sperber et al., 2019), we hypothesized that apraxic deficits in patients with AD are associated with alterations in motor and praxis-related functional brain networks.

Such functional brain networks can be studied by examining functional connectivity (FC; Seeley et al., 2009). FC has not yet been employed for studying the neural mechanisms underlying apraxic deficits in AD patients, but FC changes have been explored in studies on stroke-related apraxia. For example, a study investigated the static FC in chronic left-hemisphere stroke patients with apraxia using resting-state functional magnetic resonance imaging (fMRI; Watson et al., 2019). The stroke patients' accuracy of pantomiming tool use and actual tool use was associated with the interhemispheric connectivity between left-hemisphere regions known to be involved in tool use, action production, and processing (such as the left posterior middle temporal gyrus) and the corresponding right-hemisphere regions. However, these findings on static FC in stroke-related apraxia cannot be directly applied to apraxia in AD since stroke and AD differ considerably regarding their temporal characteristics (acute versus slowly progressive) and etiology (vascular versus neurodegenerative).

Dynamic FC captures short-term changes in brain connectivity over seconds, providing insights into neural network flexibility (Allen et al., 2014; Calhoun et al., 2014; Chang and Glover, 2010). Unlike static FC, which reflects the averaged connectivity across the entire scan (typically lasting minutes), dynamic FC allows for detecting nuanced changes that would otherwise remain obscured. Moreover, it captures recurring connectivity patterns essential for understanding the temporal fluctuations of the brain's intrinsic functional organization. Therefore, dynamic FC is more sensitive in detecting abnormalities in various neuropsychiatric disorders. For example, a dynamic FC study in patients with AD demonstrated that previously observed group differences regarding altered static connectivity in the anterior and posterior default mode network (DMN) could be explained by a change in temporal dynamic measures, i.e., increased dwell times in the anterior and decreased dwell times in the posterior DMN (Jones et al., 2012). It is increasingly assumed that dynamic connectivity measures are relevant for behavior (Vidaurre et al., 2021) and cognition (Madhyastha et al., 2015; Sadaghiani et al., 2015) and could potentially serve as clinical indicators (Lurie et al., 2020; Preti et al., 2017), e.g., to predict motor recovery after stroke (Bonkhoff et al., 2021a, 2021b). Altered dynamic connectivity allows differentiating AD patients from healthy participants and predicts disease progression in AD by identifying patients with mild cognitive impairment and faster cognitive decline (Jing et al., 2023).

Since apraxia is a network-level disorder involving widely distributed cortical regions and their connections, i.e., the motor and praxis-related functional brain networks, investigating the temporal dynamics of the functional coupling between these networks may be particularly suited to capture the neural mechanisms underlying apraxic symptoms. Therefore, for the first time, we employed FC analyses in patients with biomarker-confirmed AD pathology and apraxia to investigate how static and dynamic FC in motor and praxis-related networks differ between AD patients with apraxia and healthy controls.

2. Materials and methods

2.1. Participants

We recruited 14 individuals with biomarker-confirmed AD pathology (3 females, mean age = 68.1 years, standard deviation = 11.7 years). Patients were recruited from the interdisciplinary Center for Memory Disorders (ZfG; 'Zentrum für Gedächtnisstörungen') headed by the Departments of Neurology and Psychiatry of the University Hospital Cologne.

Patients were screened according to the following two criteria: age above 50 years and Alzheimer's clinical syndrome according to National Institute on Aging and Alzheimer's Association (NIA-AA) research framework (Jack et al., 2018). The following two inclusion criteria were applied: positive biomarkers for Alzheimer's pathology in cerebrospinal fluid (CSF) or positron emission tomography (PET, i.e., positive phospho-tau and amyloid biomarkers, A+T +) and presence of apraxia operationalized by abnormal results in the Cologne Apraxia Screening (KAS). The exclusion criteria were as follows: (i) suspected other forms of dementia than AD; (ii) other conditions responsible for cognitive or motor abnormalities, such as stroke, Parkinson's disease, multiple sclerosis, epilepsy, or normal pressure hydrocephalus; (iii) incapacity to give informed consent; (iv) any contraindications to MRI.

As a healthy control group, 14 individuals (5 females, mean age = 67.6 years, standard deviation = 9.3 years) were recruited according to the following criteria: (i) no reported subjective memory decline; (ii) no neurological or psychiatric conditions; (iii) MMSE scores more than or equal to 26; (iv) no intake of medication affecting the central nervous system.

All 28 participants were right-handed participants as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the local ethics committee of the Medical Faculty of the University of Cologne. All participants provided written informed consent. The study was conducted under the Declaration of Helsinki.

2.2. Neuropsychological assessment

Global cognitive function was classified using the Mini-Mental State Examination (MMSE; Folstein et al., 1975). For this study, the cut-off was set to 26 points, i.e., a MMSE score below 26 was considered to indicate cognitive impairment. Additionally, the Cologne Neuro-psychological Screening for Stroke Patients (KöpSS) was employed to comprehensively assess eight cognitive domains, including the domains language and visuo-spatial functions. Abnormal results were identified after adjusting the KöpSS raw scores with respect to age and education norms (Latarnik et al., 2025). Depressive symptoms were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979).

2.3. Motor assessment

Additionally, both groups underwent a comprehensive motor assessment (Wunderle et al., 2024), comprising the following tests: maximum grip strength (Volz et al., 2016), maximum finger-tapping-frequency (Wang et al., 2009), the Purdue Pegboard Test (Reddon et al., 1988), the Jebsen-Taylor Hand Function Test (Jebsen et al., 1969), and the Action Research Arm Test (Lyle, 1981).

2.4. Apraxia assessment

The apraxia assessment was performed using the KAS (maximum score = 80 points, cut-off value ≤ 76 points; Dovern et al., 2012; Weiss et al., 2013). The KAS is a validated test for assessing apraxic symptoms in stroke patients. It has also been used effectively for evaluating apraxia in mild dementia as documented by clinical (Johnen et al., 2015) and imaging studies (Johnen et al., 2016). It consists of four subtests that examine bucco-facial and arm/hand gestures in the context of two tasks, namely pantomime of object use and gesture imitation. Based on the separate cut-off values for the effectors and tasks (i.e., less than or equal to 38 of 40 points; Kusch et al., 2018), the KAS was utilized to evaluate specific apraxic deficits in pantomiming and imitation as well as bucco-facial and limb apraxia and relate those to potential alterations of static and dynamic connectivity in AD.

2.5. MRI acquisition

Magnetic resonance images were acquired using a Siemens MAGNETOM Prisma 3 Tesla scanner (Siemens Medical Solutions; Erlangen, Germany). For resting-state fMRI, participants were instructed to minimize motion throughout the measurement period of 9 min and 52 s. They were asked not to fall asleep, keep their eyes open and fixate a white cross presented on the mirrored screen in front of them. Participants were asked to let their thoughts wander. The following gradient echo-planar imaging (EPI) parameters were applied: repetition time = 0.8 s, echo time = 0.037 s, field of view = 208 mm, 72 axial slices, 2.0 mm^3 isometric voxel size, flip angle = 52°, 740 volumes. Additionally, we recorded three-dimensional T1-weighted gradient-echo sequence images (MP RAGE, repetition time = 2.5 s, echo time = 2.22 ms, field of view = 241 mm, 208 axial slices, 0.94 mm^3 isometric voxel size, flip angle = 7°) for EPI co-registration.

2.6. Preprocessing of resting-state fMRI

Resting-state fMRI data were preprocessed using fMRIPrep version 23.1.4 (Esteban et al., 2019). Before preprocessing, the initial five volumes of each scan were discarded to ensure complete saturation of the magnetic field. For all remaining 735 volumes per subject, the following steps were applied: head motion estimation and correction, slice-timing correction, susceptibility distortion correction, skull stripping, co-registration, and normalization into MNI space. The mean and maximum framewise displacement (FD) for each subject's scan was computed as a measure of head motion (Jenkinson and Smith, 2001; Power et al., 2014). Finally, preprocessed fMRI images were smoothed with a Gaussian filter of 5 mm at full-width-at-half-maximum using Statistical Parametric Mapping (SPM 12; Wellcome Centre for Human Neuroimaging, London, UK), implemented in Matlab version 2023b (Mathworks Inc.; MA, USA). Head motion estimations of all datasets, as quantified by mean FD values, were included as covariates in the subsequent analyses.

2.7. Static and dynamic connectivity

For the analysis of functional connectivity (FC), we used the GIFT Toolbox Version 4.0 (https://trendscenter.org/software/gift/) implemented in SPM 12. Initially, preprocessed resting-state fMRI data were entered into an independent component analysis (ICA) to extract components that represent connectivity networks (Du and Fan, 2013; Lin et al., 2009). Using the Neuromark_fMRI_2.1 template (Iraji et al., 2022), which was built upon datasets of over 57.000 individuals (available in the GIFT Toolbox and at https://trendscenter.org/data/), a total of 105 intrinsic components were used to constrain the ICA spatially. Thus, spatial biases due to artifacts were minimized, while robustness to noise and sustained individual adaptability were ensured (Du et al., 2016; Salman et al., 2019). Using a back-reconstruction algorithm, this group information guided ICA yielded spatial maps and corresponding time courses for each component per participant.

Since our study primarily focused on the analysis of connectivity in patients with apraxia as a cognitive motor deficit, we focused on intrinsic components related to basic and complex motor functions as well as specific components comprising praxis networks. Components with low ratios of low- to high-frequency spectra, which indicate a poor signal-to-noise ratio, were excluded. Instead, we opted for components as intrinsic connectivity networks (ICNs) that exhibit a high fractional amplitude of low-frequency fluctuations (fALFF), which are presumably markers of spontaneous neural activity in the corresponding regions of the brain (Zou et al., 2008). Based on these criteria, we identified 10 ICNs: (i) left primary sensorimotor cortex; (ii) right primary sensorimotor cortex; (iii) bilateral supplementary motor area (SMA); (iv) bilateral premotor cortex (PMC); (v) left cerebellum; (vi) right cerebellum; (vii) bilateral IPS; (viii) bilateral IPL; (ix) left fronto-parietal network; (x) right fronto-parietal network (Figure 1). Our (apraxia) assessments were based on verbal commands and visual representations, thus we included networks comprising the primary visual and auditory cortices. We assigned these networks to three network domains (see Figure 1): the primary domain (which should not be affected by apraxia), the action domain (comprising motor regions associated with complex motor functions), and the praxis domain (of particular interest in the study of apraxia; Schmidt et al., 2022). Before further analysis, blood-oxygen-level-dependent (BOLD) signal time courses were detrended, despiked using 3Ddespike, filtered by a low-pass filter with a high-frequency cut-off of 0.15 Hz, and normalized for variance (Rachakonda et al., 2007).

For the analysis of static FC, we employed the MANCOVAN toolbox as part of the GIFT Toolbox. We examined static FC strength between networks. Age, sex, years of education, and FD were regressed out as covariates in all analyses. Connectivity strength was computed using mean Pearson's pairwise correlations and reported as Fisher's Z-transformed correlations. Dynamic functional connectivity was analyzed using a sliding window approach (Allen et al., 2014; Calhoun et al., 2014; Damaraju et al., 2014; Sakoğlu et al., 2010) with a window size of 44 s, a Gaussian window alpha of three, and a window shift of 0.8 s (one repetition time). Thus, each measurement was divided into 657 individual windows. Across all participants and scans, dynamic connectivity was computed for 657 x 28 = 18,396 sliding windows (number of sliding windows per participant x number of participants = number of sliding windows overall). We selected parameter settings based on prior research suggesting that window widths between 30 and 60 s allow for effective and reliable estimation of dynamic FC without noise dominance (Allen et al., 2014; Preti et al., 2017). Within each window, dynamic FC was computed using the l1-regularized precision matrix. Once again, age, sex, years of education, and FD were regressed out as covariates in all analyses. Similar to the computation of static FC, dynamic FC strength was calculated as Fisher Z-transformed correlations between networks. To group similar connectivity patterns during the windows, we employed k-means clustering (Allen et al., 2014; Calhoun et al., 2014), resulting in distinct dynamic connectivity states. Calculating an optimal cluster size, using (i) the silhouette score (Rousseeuw, 1987) and (ii) Ray Turi criterion (Ray and Turi, 1999) based upon the cluster validity index, as well as (iii) a state frequency of more than 10 %, revealed an optimal number of $k = 2$ states (see Figure S1).

2.8. Statistics

We used Python version 3.11.3 and JASP version 0.18.3 (University of Amsterdam, Netherlands) for statistical analyses. For all statistical analyses, a significance level of $P < 0.05$ was set. False-Discovery Rate (FDR)-correction at a significance level of $P < 0.05$ was applied to account for multiple comparisons (Benjamini and Hochberg, 1995). Parametric results are depicted as mean (standard deviation), while non-parametric results are presented as median (range). For

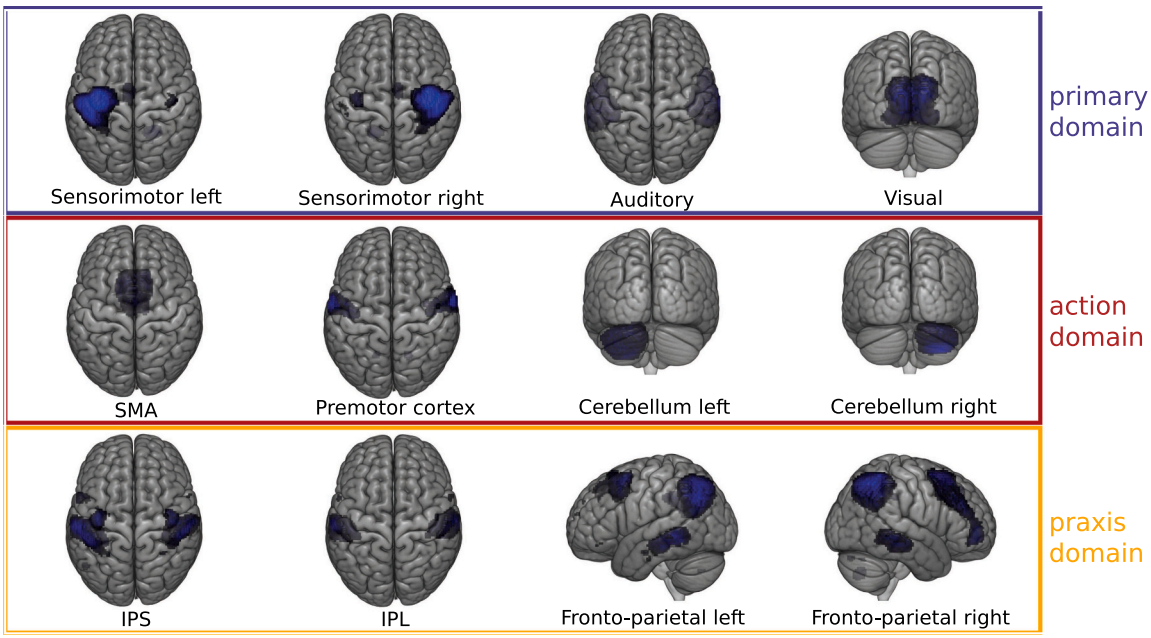

Fig. 1. Visual depiction of the analyzed intrinsic connectivity networks (ICNs). The spatial maps of the 12 analyzed intrinsic connectivity networks (ICNs) are shown as brain renderings for the entire study population ($n = 28$), consisting of 14 individuals diagnosed with Alzheimer's disease and 14 healthy participants. The ICNs were categorized into three different domains: sensorimotor domain (purple), action domain (red), praxis domain (orange).

demographic, clinical, and behavioral data, group differences were examined using independent Student's t-tests where conditions for parametric testing were met, otherwise differences were assessed using non-parametric Mann-Whitney U tests.

2.8.1. Static and dynamic connectivity analysis

Regarding static FC, we examined group differences in connectivity strength between ICN pairs using independent Student's t-tests. For dynamic FC, we analyzed connectivity strength between ICN pairs employing independent Student's t-tests. Two-way analyses of variances (ANOVAs), each with the between-subject factor group (patients, controls) and the within-subject factor state (state 1, state 2), were performed to evaluate temporal measures of dynamic connectivity: the fraction time (i.e., the proportion of total time spent in one state) and the dwell time (i.e., the mean time spent in a given state without switching to another state). FDR-corrected post-hoc t-tests were conducted in case of significant ANOVA results. Additionally, we investigated group differences in the number of transitions between states using an independent Student's *t*-test.

2.8.2. Correlating dynamic connectivity features with apraxia scores

Within both the group of AD patients and healthy controls, we explored whether differences in static and dynamic FC were associated with specific apraxic deficits assessed by the KAS. For correlation analysis, we evaluated the overall KAS score and the separate scores for tasks (pantomime, imitation) and effectors (bucco-facial, arm/hand). We focused on static and dynamic connectivity and temporal measures in dynamic FC from the preceding analyses that revealed significant differences between AD patients and healthy controls (HC). Correlations were controlled for global cognitive function, temporal differences between measurements, language function, and visuo-spatial function using partial correlations. We used Spearman correlations when normality was not met according to the Shapiro-Wilk test. Otherwise, we calculated Pearson correlations.

2.8.3. Hierarchical multiple regression analysis

We conducted a hierarchical linear regression analysis to explore whether the observed associations of static and dynamic FC measures and KAS scores can also be used to predict apraxic deficits in AD patients. For this analysis, we defined the measures of performed partial correlations as independent variables (i.e., measures of static and dynamic FC) and the corresponding KAS score as the dependent variable. In the first regression, for each significantly associated KAS score from the correlation analysis, we included the respective independent variables at the hierarchical levels of the models. Each model's fit was evaluated using the Akaike Information Criterion (AIC), a goodness-of-fit measure that penalizes model complexity by accounting for the number of predictors (Akaike, 1974). We then compared the models and selected the one with the lowest Akaike score, indicating the best fit to the data. In a second regression, the same dependent variable was retained, while on the first level, we included variables to control for global cognitive function and temporal differences between measurements (in days). On the second level, we incorporated the variables that had been part of the model with the optimal fit from the first regression as independent variables. This way, it was possible to control for the influence of confounding variables sequentially while simultaneously examining the effects of the variables of interest.

2.9. Data availability

The data supporting this study's findings are findable in the CRC1451 data registry (https://www.crc1451.uni-koeln.de/) and can be obtained from the corresponding author upon reasonable request and after approval by the local ethic authorities.

3. Results

3.1. Demographic and clinical characteristics

Patients with AD and healthy controls did not differ significantly in terms of age, sex, years of education, and handedness as assessed by the laterality quotient of the EHI. Table 1 provides an overview of the demographic information. Furthermore, there were no significant group differences regarding the framewise displacement (FD) during resting-state fMRI (AD patients: mean FD = 0.26 mm, standard deviation = 0.14 mm; HC participants: mean FD = 0.19 mm, standard deviation =

Table 1
Demographic characteristics of the study population.

Category	Patients with Alzheimer's disease ($n = 14$)	Healthy controls ($n = 14$)	P
Age [years][1]	68.1 (11.7)	67.6 (9.3)	0.915
Sex [m/f]	11/3	9/5	0.676
Years of education [years]	14 (13–21)	18 (13–21)	0.141
Laterality quotient [%]	100 (80–100)	100 (58–100)	0.079

The table depicts the demographic characteristics of the study population, divided into the groups of individuals with Alzheimer's disease and healthy controls. Descriptive data for each group are provided as means (standard deviations) for parametric data[1] and median (range) for non-parametric data. Age was compared between the groups using Student's t-tests. While Mann-Whitney U tests were employed to compare years of education and laterality quotient between the groups, sex frequencies were compared using a chi-squared test.

0.07 mm; $t(26) = –1.637$, $P = 0.114$, independent Student's t-test). The biomarker status for each patient can be found in the supplementary material (see Table S1). Six patients were taking acetylcholinesterase inhibitors (donepezil = 5, galantamine = 1) at the time of study conduction.

3.2. Neuropsychological assessment

All patients presented with positive biomarkers for Alzheimer's pathology, whereas none of the healthy controls who underwent tau-PET imaging (n = 12) showed pathological tracer uptake. Within the group of 14 patients with biomarker-verified AD, 10 individuals exhibited symptoms of cognitive impairment (i.e., scores equal to or lower than 25 points in the MMSE). In contrast, all individuals within the group of healthy controls exhibited test results indicative of intact cognitive functioning (i.e., scores greater than 25 points in the MMSE). The MMSE score of the AD patients (median: 23.5, range: 18–29) differed significantly from that of the healthy control group (median: 30, range = 27–30; $U = 192.5$, $P_{FDR} = < 0.001$, Mann-Whitney U test). While there was also a significant group difference for the KöpSS score, the two groups did not differ significantly regarding depressive symptoms as evaluated by the MADRS (see Table S2A in the supplementary material).

3.3. Motor assessment

The supplementary material gives detailed results of the motor assessment (see Table S2B). No differences in basic motor functions were observed between the two groups. However, about complex motor functions, controls performed significantly better than the AD patients in the Purdue Pegboard Test ($t(26) = 3.192$, $P_{FDR} = 0.020$) and in the Jebsen-Taylor Hand Function Test ($t(26) = –2.753$, $P_{FDR} = 0.041$) when using their right dominant hand.

3.4. Apraxia assessment

All current 14 AD patients exhibited apraxia, as evidenced by abnormal results in at least one subtest of the KAS. One patient with AD showed apraxic deficits for bucco-facial gestures only. 13 AD patients showed apraxic deficits for arm/hand gestures, i.e., limb apraxia. Of the 13 AD patients with limb apraxia, five patients were also impaired when pantomiming the use of objects involving bucco-facial gestures. Another patient with limb apraxia showed an additional impairment in imitating bucco-facial gestures.

This pattern of apraxic deficits was reflected in the patients' KAS scores. The AD patients achieved similar scores for the two tasks (pantomiming: median = 36 points, range = 32–40 points; imitation: median = 38 points, range: 28–40 points; $U = 101.5$, $P = 0.888$, Mann-Whitney U test), but they scored significantly less points in the KAS subtests involving arm/hand gestures (median = 36 points, range = 24–40 points) than in those KAS subtests involving bucco-facial gestures (median = 39.5 points, range = 34–40 points; $U = 40.5$, $P = 0.008$, Mann-Whitney U test).

3.5. Static and dynamic functional connectivity

Across all participants, analysis of static FC between networks revealed strong positive and negative connectivity strengths between motor networks of the primary (i.e., sensorimotor), action (i.e., SMA, PMC, cerebellar), and praxis (i.e., IPS, IPL) domains with each other. In contrast, correlations between the auditory, visual, and fronto-parietal networks and any other network were markedly weak (see Figure 2A). Comparing static connectivity strength between the two groups, HC demonstrated significantly stronger connectivity between the left fronto-parietal network and the IPS and SMA networks, between the SMA and IPL network, and between the auditory and left sensorimotor networks. In contrast, AD patients presented stronger connectivity between the visual network and the IPS, IPL and PMC network, and between the left sensorimotor and left fronto-parietal network ($P < 0.050$, see Figure 2).

For the analysis of dynamic FC in the entire study sample, k-means clustering suggested a division of the connectivity windows into two dynamic states (see Figure 3). They were characterized by similar patterns concerning positive and negative connectivity between networks that were, however, varied in the strength of their connectivity. The second state featured pronounced connectivity strength between network pairs, while in the first state connectivity was markedly weak. Based on the quantitative analysis of segregation and integration parameters of the two dynamic states (see supplementary results of domain-wide segregation and integration), we will refer to the weakly connected state 1 as the segregated state and the strongly connected state 2 as the integrated state.

Regarding significant group differences in dynamic FC strength, the group of HC featured more robust connectivity between networks in the action domain, i.e., between the PMC and SMA, and between the PMC and right cerebellar ICNs in the segregated state 1 (see Figure 4A). In this segregated state 1, AD patients exhibited stronger connectivity between the visual and IPL ICNs, between the visual and SMA ICNs, and between right fronto-parietal and left sensorimotor ICNs. In the integrated state 2, significantly stronger connectivity was observed between both cerebellar ICNs and the IPL ICNs as well as between the left cerebellar and PMC ICNs in HC and between the visual and SMA, IPL and IPS ICNs in AD patients (see Figure 4B). Notably, the group differences in connectivity strength between the visual ICN and the IPL and SMA ICNs were more pronounced in the integrated state 2 than in the segregated state 1.

Across all participants (n = 28), we evaluated dynamic FC in a total of 18,396 sliding windows (657 windows × 28 participants). Considering temporal characteristics, the segregated state 1 occurred 10,730 times (58.3 %) across all measurements of the entire study population, while the integrated state 2 occurred 7666 times (41.7 %). All HC entered both dynamic states throughout their respective fMRI measurements, but only 13 AD patients visited the integrated state 2. Figure 5A illustrates that AD patients transitioned significantly less frequently between the two states compared to controls ($t(26) = –4.562$, $P < 0.001$). Figure 5B presents the mean fraction times per state and group. For this temporal dynamic connectivity measure, an ANOVA revealed no significant main effect of the factor group but a significant main effect of the factor state ($F(1, 54) = 5.773$, $P = 0.02$, $\eta^2 = 0.082$) and a significant state x group interaction ($F(1, 54) = 12.765$, $P = < 0.001$, $\eta^2 = 0.181$). Post-hoc t-tests indicated that AD patients had a significantly higher fraction time in the segregated state 1 compared to the integrated state 2 ($P_{FDR} = < 0.001$), i.e., over the entire scan duration, AD patients spent more time in the weakly connected state 1. In contrast, no such difference in the fraction time between the two states was observed for HC ($P_{FDR} = 0.841$). For dwell times, i.e., the mean time

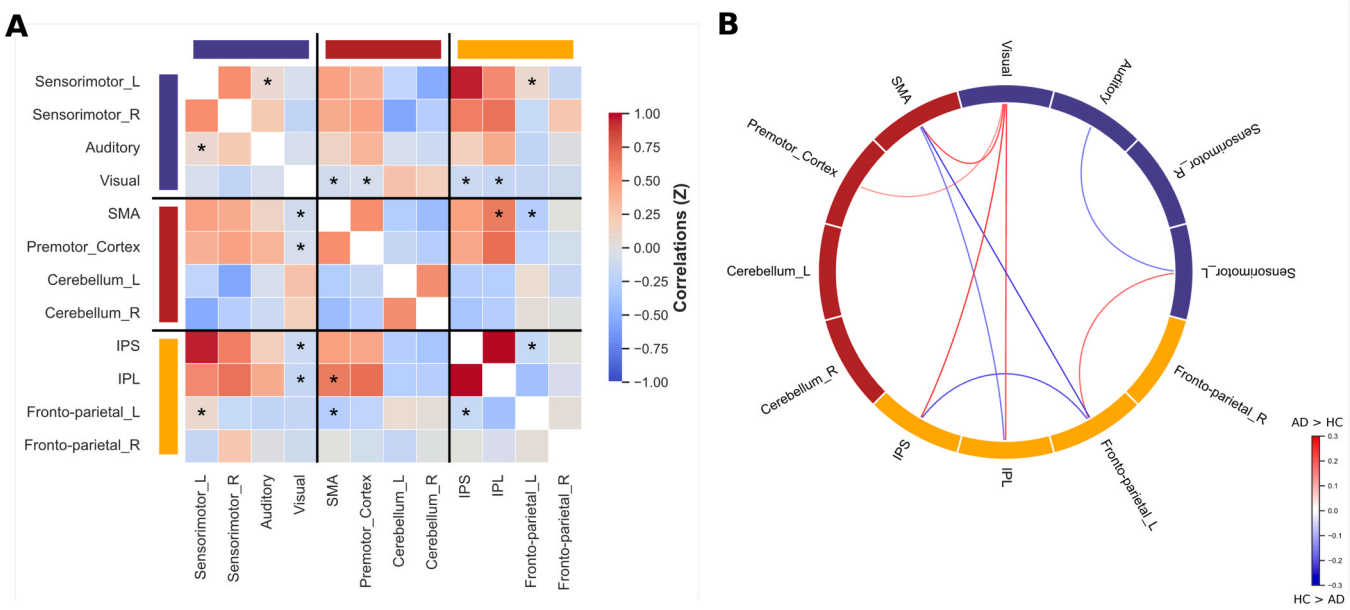

Fig. 2. Static functional connectivity analysis. (A) The static connectivity matrix, averaged over all patients with Alzheimer's disease (AD) and healthy control participants (HC), depicts pairs of high (red) and low (blue) connectivity as Z-transformed Pearson correlations between all analyzed intrinsic connectivity networks (ICNs). The colored bars at the top and left side correspond to the three domains presented in Figure 1 (purple: sensorimotor domain, red: action domain, orange: praxis domain). Asterisks in the connectivity matrix indicate significant group differences regarding static connectivity between ICNs (independent Student's t-tests: level of significance, $P < 0.05$). **(B)** A circle plot depicting the significant static connectivity differences between groups. The colored circle components in the circle plot correspond to the three domains presented in Figure 1. Red lines indicate significantly stronger connectivity in AD patients compared to HC, while blue lines indicate significantly stronger connectivity in HC compared to patients (independent Student's t-tests: level of significance, $P < 0.05$). The connectivity between the left fronto-parietal ICN and the ICNs comprising the intraparietal sulcus (IPS) and the supplementary motor area (SMA), between the SMA and the inferior parietal lobule (IPL) ICNs, as well as between the auditory and left sensorimotor ICNs were increased in HC (blue lines), while the connectivity between the visual ICN and ICNs comprising the IPS, IPL, and PMC, as well as the connectivity between the left fronto-parietal ICN and the left sensorimotor ICN were increased in AD patients (red lines).

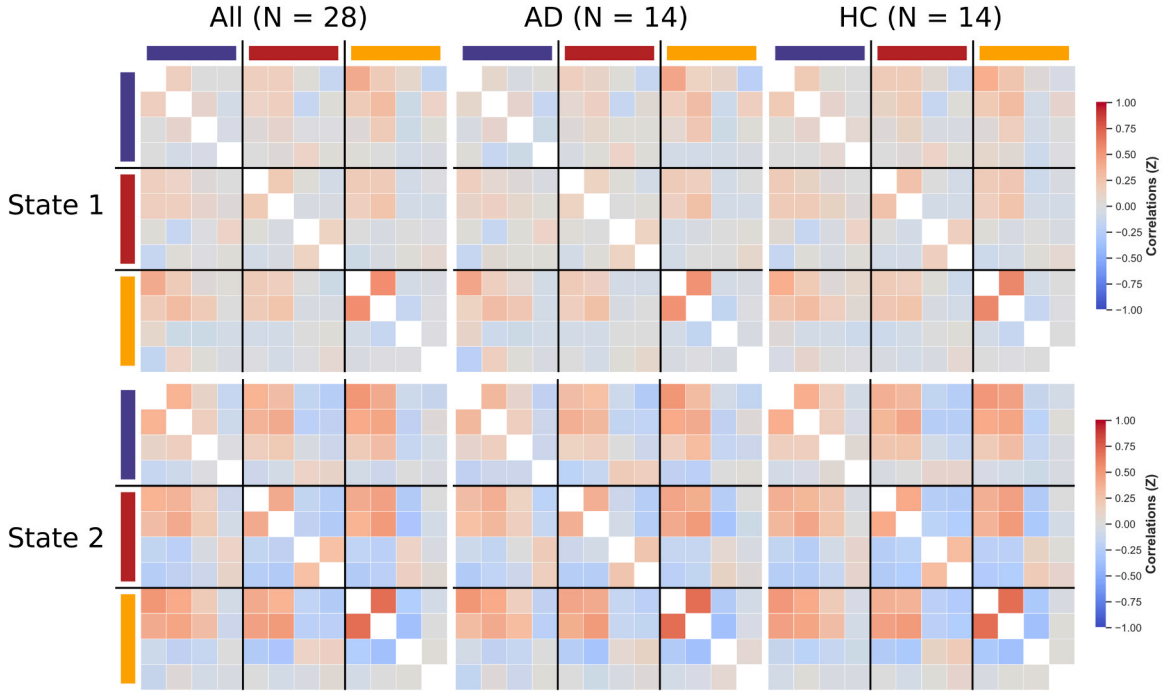

Fig. 3. Dynamic functional connectivity matrices. The dynamic connectivity matrices of the first (segregated) and second (integrated) dynamic states are shown for the entire study population, as well as for patients with Alzheimer's disease (AD) and healthy control participants (HC) separately. Depicted are pairs of high (red) and low (blue) connectivity between all analyzed intrinsic connectivity networks (ICNs). The colored bars at the top and left side correspond to the three domains presented in Figure 1 (purple: sensorimotor domain, red: action domain, orange: praxis domain).

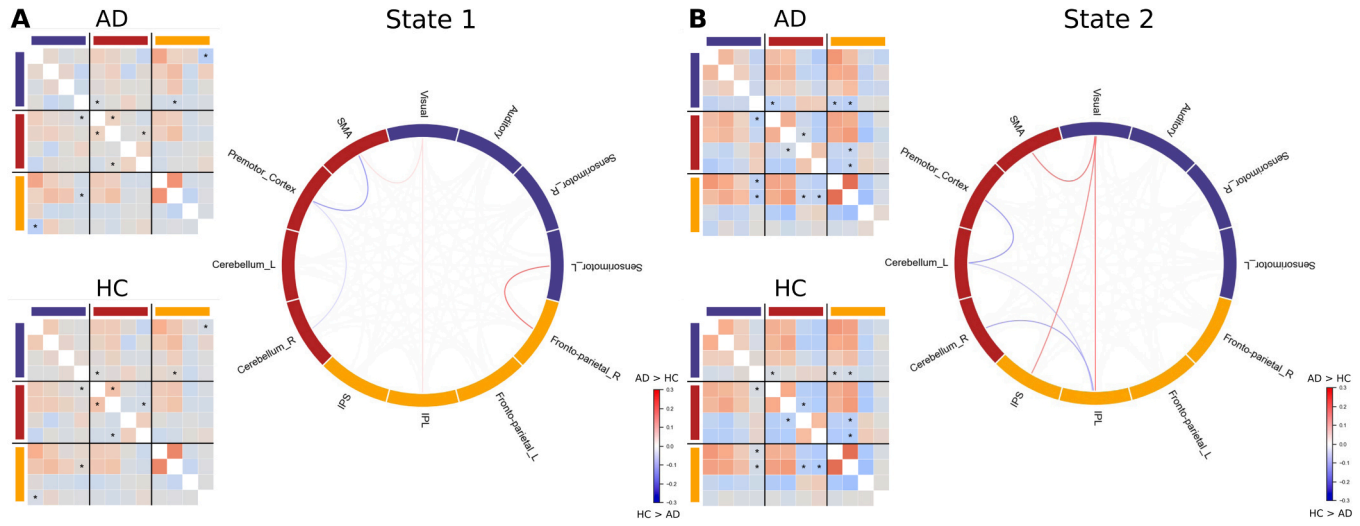

Fig. 4. Significant dynamic functional connectivity differences between groups. Dynamic connectivity matrices depicting Z-transformed Pearson correlations between all intrinsic connectivity networks (ICNs) for each dynamic state, as well as the corresponding circle plots of significant dynamic connectivity differences between the group of patients with Alzheimer's disease (AD) and healthy control participants (HC) are shown for the first (segregated) dynamic connectivity state (**A**) and second (integrated) dynamic connectivity state (**B**). The colored bars at the top and left side of the connectivity matrices correspond to the three domains presented in Figure 1 and the colored circle components in the circle plot (purple: sensorimotor domain, red: action domain, orange: praxis domain). Significant group differences in dynamic functional connectivity between ICNs are indicated with asterisks in the respective connectivity matrices and lines between the corresponding connectivity networks in the circle plots, where red lines indicate stronger connectivity in AD patients compared to HC. In contrast, blue lines indicate significantly stronger connectivity in HC compared to patients (independent Student's t-tests: level of significance, $P < 0.05$). **(A)** Connectivity differences in the segregated dynamic connectivity state 1. The group of HC presented stronger connectivity between the premotor cortex INC and the supplementary motor area (SMA) ICN and the right cerebellar ICN. In contrast, AD patients exhibited stronger connectivity between the visual ICN and the inferior parietal lobe (IPL) and SMA ICNs and between the right fronto-parietal ICN and the left sensorimotor ICN. **(B)** Connectivity differences in the integrated dynamic connectivity state 2. While the group of HC exhibited increased connectivity between both cerebellar ICNs and the IPL ICN as well as between the left cerebellar and premotor INCs, AD patients showed stronger connectivity between the visual ICN and the SMA, IPL, and IPS ICNs.

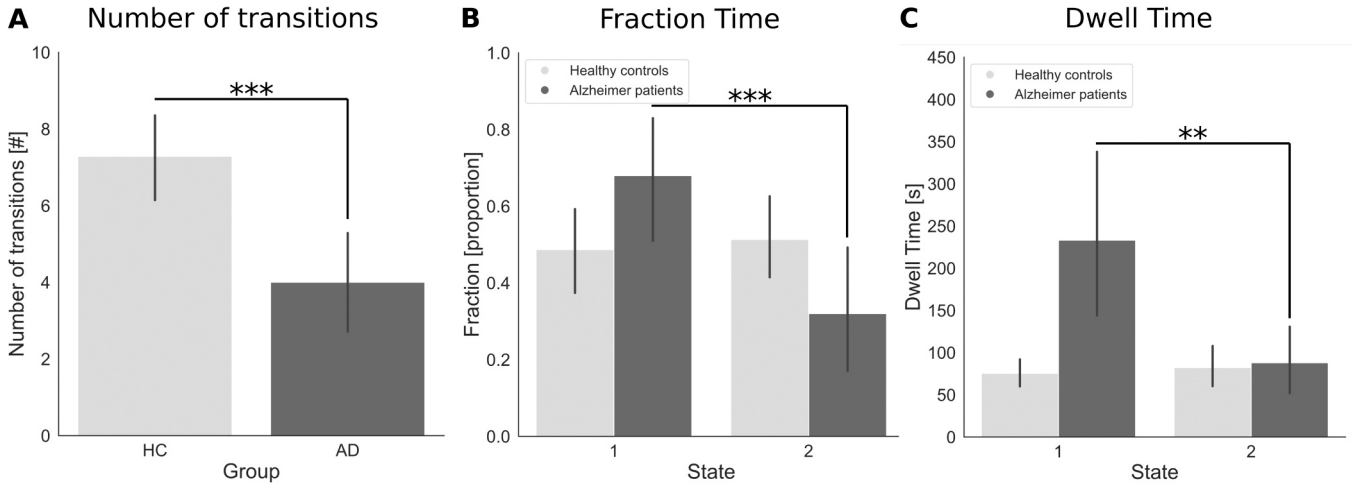

Fig. 5. Temporal measures of dynamic functional connectivity. Depicted are the number of transitions (A), the fraction times (B), and the dwell times (C) for the patients with Alzheimer's disease (AD, dark gray) and healthy control participants (HC, light gray). **(A)** Number of transitions. Compared to HC, AD patients switched significantly less often between the two dynamic connectivity states. **(B)** Fraction times. AD patients spent significantly more time in the segregated dynamic connectivity state 1 compared to the integrated dynamic connectivity state 2 over the entire scan duration. **(C)** Dwell times. AD patients dwelled significantly longer in the segregated dynamic connectivity state 1 in consecutive dynamic windows over the entire scan duration compared to HC in the same state, as well as to compared to AD patients in the integrated dynamic connectivity state 2. Asterisks indicate statistically significant differences after post-hoc t-tests: ** = $P < 0.01$, *** = $P < 0.001$.

spent in a given state without switching to another state (see Figure 5C), an ANOVA revealed a significant effect of the factors state ($F(1, 53) = 5.507$, $P = 0.023$, $\eta^2 = 0.078$) and group ($F(1, 53) = 6.070$, $P = 0.017$, $\eta^2 = 0.086$) as well as a significant state x group interaction ($F(1, 53) = 8.023$, $P = 0.007$, $\eta^2 = 0.113$). Post-hoc t-tests indicated a significantly longer dwell time of AD patients compared to controls in the segregated state 1 ($P_{FDR} = 0.002$), as well as compared to AD patients in the integrated state 2 ($P_{FDR} = 0.004$). In contrast, HC did not differ concerning their dwell time in state 1 versus state 2 ($P_{FDR} = 0.986$).

3.6. Associations between connectivity measures and apraxia scores

In AD patients and healthy controls, we evaluated associations between the different KAS scores and those static and dynamic FC

strengths that had revealed significant group differences. These correlation analyses were controlled for the time between the apraxia assessment and the MRI measurement (in days), global cognitive function (as assessed by the MMSE), language function (as operationalized by the language domain score of the KöpSS), and visuo-spatial functions (as operationalized by the KöpSS domain score for visuo-spatial functions). Within the group of AD patients, the static connectivity between the visual ICN and the IPL ICN was significantly associated with both KAS imitation scores and the KAS arm/hand scores (see Table 2). Thus, stronger connectivity between these two ICNs was accompanied by less severe apraxic deficits concerning arm/hand gestures and gesture imitation. In contrast, we observed no significant associations between static connectivity strength and the different KAS scores within the healthy control participants. Regarding dynamic FC, the connectivity between the visual and IPL ICNs in the segregated state 1 was significantly associated with the KAS imitation scores of AD patients (see Table 2). Thus, stronger connectivity between these two ICNs in the weakly connected state 1 was accompanied by less severe apraxic imitation deficits in patients with AD. In healthy control participants, the connectivity between right cerebellar and premotor ICNs in the segregated state 1 was significantly positively associated with the KAS pantomime, KAS bucco-facial, and total KAS scores. Thus, stronger connectivity between these two ICNs in the weakly connected state 1 was accompanied by better performance in the KAS while staying within the score range above the cut-off of the KAS.

Further, we assessed the association between the apraxia scores and the temporal dynamic FC measures (i.e., the number of transitions, as well as the fraction and dwell time of the two dynamic states) that had revealed significant group differences. Again, these correlation analyses were controlled for the time between the apraxia assessment and the MRI measurement (in days), global cognitive function (as assessed by the MMSE), language function (as operationalized by the language domain score of the KöpSS), and visuo-spatial function (as operationalized by the KöpSS domain score for visuo-spatial function). For the AD patients, the correlations of the number of transitions between the two dynamic states with the KAS imitation ($r = 0.695$, $P_{FDR} = 0.095$, Pearson correlation) and KAS arm/hand scores ($r = 0.719$, $P_{FDR} = 0.095$, Pearson correlation) revealed a statistical trend. These findings suggest that more severe apraxic deficits in imitation and arm/hand gestures were associated with fewer transitions between the two dynamic states. The KAS imitation scores of the AD patients were negatively associated with the fraction times of the segregated state 1 and positively associated with the fraction times of the integrated state 2 (see Table 3A).

Table 2
Correlation analysis between static and dynamic connectivity and apraxia scores.

Correlation	sFC: visual – IPL		dFC State 1: visual – IPL	
	Coefficient	P_{FDR}	Coefficient	P_{FDR}
KAS total	0.641	0.105	0.457	0.360
KAS pantomime	0.120	0.817	–0.232	0.685
KAS imitation	**0.762**	**0.043***	**0.851**	**0.020***
KAS bucco-facial	0.091	0.817	–0.110	0.777
KAS arm/hand	**0.848**	**0.020***	0.728	0.065

For Alzheimer's disease (AD) patients with apraxia (n = 14), the table depicts the results of the FDR-corrected correlation analyses between the scores of the Cologne Apraxia Screening (KAS) and the static functional connectivity (sFC) as well as the dynamic functional connectivity in the segregated state 1 (dFC) between the intrinsic connectivity networks (ICNs) involving visual regions and the inferior parietal lobule (IPL). These correlation analyses were controlled for the time between the apraxia assessment and the MRI measurement (in days), global cognitive function (as assessed by the MMSE), language function (as operationalized by the language domain score of the KöpSS), and visuo-spatial function (as operationalized by the KöpSS domain score for visuo-spatial function). For all reported correlation analysis results, we used Pearson correlations. Asterisks indicate statistically significant differences: * = $P_{FDR} < 0.05$.

Table 3A
Correlation analysis between fraction times and apraxia scores.

Correlation	Fraction Time State 1		Fraction Time State 2	
	Coefficient	P_{FDR}	Coefficient	P_{FDR}
KAS total	–0.272	0.728	0.272	0.728
KAS pantomime	0.378	0.728	–0.378	0.728
KAS imitation	**–0.858**	**0.015***	**0.858**	**0.015***
KAS bucco-facial	–0.031	0.937	0.031	0.937
KAS arm/hand	–0.213	0.728	0.213	0.728

Table 3B
Correlation analysis between dwell times and apraxia scores.

Correlation	Dwell Time State 1		Dwell Time State 2	
	Coefficient	P_{FDR}	Coefficient	P_{FDR}
KAS total	–0.507	0.273	0.018	0.966
KAS pantomime	0.144	0.889	–0.455	0.643
KAS imitation	**–0.914**	**0.003****	0.693	0.285
KAS bucco-facial	–0.040	0.918	0.138	0.930
KAS arm/hand	–0.576	0.263	–0.244	0.930

The tables depict the results of the FDR-corrected correlation analysis between dynamic functional connectivity (FC) features (i.e., fraction and dwell times) and the Cologne Apraxia Screening (KAS) scores of AD patients with apraxia ($n = 14$). The correlation analyses of the mean fraction times (Table 3A) and the dwell times (Table 3B) in the first and second dynamic states were controlled for the time between the apraxia assessment and the MRI measurement (in days), global cognitive function (as assessed by the MMSE), language function (as operationalized by the language domain score of the KöpSS), and visuo-spatial function (as operationalized by the KöpSS domain score for visuo-spatial function). For all reported correlation analysis results, we used Spearman correlations. Asterisks indicate statistically significant differences: * = $P_{FDR} < 0.05$, ** = $P_{FDR} < 0.01$.

Moreover, poorer KAS imitation scores were associated with a longer dwell time in the segregated state 1 (see Table 3B). Thus, more severe apraxic imitation deficits were associated with decreased fraction times in the integrated state 2, characterized by more pronounced connectivity, and with increased fraction and dwell times in the segregated state 1, characterized by weaker connectivity.

3.7. Prediction of apraxic deficits using connectivity measures

The hierarchical multiple regression analysis revealed that a model including the static connectivity between the visual and IPL ICNs did not predict variance in KAS arm/hand scores in AD patients (adjusted $R^2 = -0.028$, $F(1, 12) = 0.648$, $P = 0.437$). In contrast, a model including the mean fraction times of the segregated state 1 predicted the variance in KAS imitation scores (adjusted $R^2 = 0.425$, $F(1, 12) = 10.591$, $P = 0.007$). The predictive value of this model improved significantly after adding the dynamic connectivity between the visual and IPL ICNs in the segregated dynamic state 1 to the mean fraction times (adjusted $R^2 = 0.794$, $F(2, 11) = 26.094$, $P < 0.001$; R^2 change = 0.357, F change $(1, 11) = 22.566$, $P < 0.001$). The model still predicted KAS imitation scores significantly after incorporating dwell times of the segregated state 1 to the independent variables (adjusted $R^2 = 0.784$, $F(3, 10) = 16.717$, $P < 0.001$). However, the change was not significant (R^2 change = 0.008, F change $(1, 10) = 0.471$, $P = 0.508$). Estimation of the models' fit revealed that the (two-predictor) model comprising the mean fraction times of state 1 and the dynamic connectivity between visual and IPL ICNs in state 1 featured the lowest AIC of 17.078. In contrast, the (one-predictor) model, including only the fraction times of state 1, had an AIC of 30.696 and the (three-predictor) model, including fraction times and dwell times of state 1 and dynamic connectivity between visual and IPL ICNs exhibited an AIC of 18.434. Therefore, the two-predictor model showed the best fit (i.e., the lowest AIC) and thus these two predictors were incorporated into the consequent regression.

For the second regression, the model including MMSE scores and the temporal difference between measurements (in days) as covariates did not predict variance in KAS imitation scores in AD patients (adjusted $R^2 = 0.118$, $F(2, 11) = 0.648$, $P = 0.200$). This changed after adding the variables of the two-predictor model (adjusted $R^2 = 0.782$, $F(4, 9) = 12.690$, $P < 0.001$; R^2 change $= 0.596$, F change $(2, 9) = 17.804$, $P < 0.001$). While more severe apraxic imitation deficits in AD patients were significantly predicted by both higher fraction times of segregated state 1 (*beta* = – 0.494, $t = –3.482$, $P = 0.007$) and more negative connectivity between the visual and IPL ICNs in the segregated state 1 (*beta* = 0.583, $t = 4.329$, $P = 0.002$), both covariates did not have predictive power (MMSE: *beta* = 0.153, $t = 1.074$, $P = 0.311$; temporal difference between measurements: *beta* = –0.092, $t = –0.688$, $P = 0.509$).

4. Discussion

In the present study, we investigated static and dynamic FC using resting-state fMRI in a well-characterized sample of AD patients with apraxia. When compared to a matched group of healthy participants, we found significant group differences in the strengths of static and dynamic FC. In particular, apraxic AD patients exhibited stronger static and dynamic connectivity between visual and IPL ICNs. In addition, analysis of the temporal dynamic connectivity measures revealed that apraxic AD patients exhibited longer fraction and dwell times in the weakly connected, i.e., more segregated dynamic connectivity state 1. Thus, for the first time, we could demonstrate that apraxic deficits in AD patients are related to (and can be predicted by) altered static and dynamic connectivity measures. These findings provide novel insights into the neural mechanisms underlying apraxia in AD and thus help better understand the pathophysiology of this still understudied complex motor cognitive disorder. Apraxic deficits have been shown to negatively affect patients' independence in activities of daily living and overall quality of life. Identifying measures of FC specifically associated with apraxic deficits may help improve the clinical characterization of AD patients beyond classical cognitive impairments and provide clinical indicators of functional disability, enabling timely support and targeted interventions to maintain autonomy.

4.1. Assessment of motor functions and apraxia

A comprehensive motor assessment was conducted in all participants, evaluating basic (i.e., maximum grip strength, maximum finger tapping) and complex (i.e., Purdue Pegboard Test, Jebsen-Taylor Hand Function Test) motor functions. There were no significant group differences in basic motor functions between patients and controls. However, the apraxic AD patients differed significantly from the healthy participants in the timed tests assessing complex motor functions. These findings align with the notion that apraxia is not due to basic motor deficits and previous observations that AD patients can present with impaired dexterity (Gupta et al., 2024).

In the current AD patient sample, apraxic deficits (as assessed with the KAS) were particularly observed for arm/hand gestures in both tasks (i.e., gesture imitation and pantomiming the use of objects). In contrast, bucco-facial gestures were less severely affected. Thus, the current findings are consistent with previous studies reporting that in AD patients apraxic symptoms predominantly manifest as limb apraxia, specifically affecting the imitation of finger and hand gestures (Johnen et al., 2016).

4.2. Functional connectivity in action and praxis networks

We observed significant differences in static and dynamic connectivity strengths between apraxic AD patients and healthy participants for various ICN pairs. Notably, concerning static and dynamic connectivity (in both dynamic states), connectivity between two ICNs that was stronger in AD patients (compared to healthy participants) always involved one ICN of the primary domain, which includes low-level sensorimotor and visual networks typically unaffected by apraxia. In contrast, healthy individuals showed increased static and dynamic connectivity between ICN pairs that always comprised an ICN of the action or praxis domains. The action domain encompasses motor-related networks involved in movement planning and execution. In contrast, the praxis domain includes higher-order regions implicated specifically in the representation and production of skilled gestures. This altered static and dynamic connectivity pattern in AD patients with apraxia may reflect a functional disconnection of task-relevant motor and praxis-related networks. The increase in connectivity with primary regions might indicate a compensatory shift toward more basic sensorimotor and visual processing pathways, which may be insufficient to support complex gesture production.

There is only one previous study on FC in apraxia. This work analyzed static connectivity in chronic left-hemisphere stroke patients using a seed-based approach (Watson et al., 2019). The study demonstrated significant associations between performance in a pantomime task and static interhemispheric connectivity of the left superior parietal cortex, left postcentral gyrus, and left posterior medial temporal gyrus with their corresponding homologous areas in the right hemisphere. Similarly, our study revealed significant associations between apraxic deficits and altered static and dynamic connectivity. In particular, apraxic deficits of arm/hand gestures were associated with reduced static connectivity between the visual and IPL ICNs. In contrast, apraxic imitation deficits were associated with reduced static and dynamic connectivity between these two ICNs. The current findings of static and dynamic connectivity changes involving the IPL of apraxic AD patients are consistent with previous observations indicating a prominent role of IPL lesions for apraxic deficits in imitating arm/hand gestures in left-hemisphere stroke patients (Schmidt et al., 2022). Moreover, our findings suggest that increased connectivity, i.e. increased information flow, between visual and IPL ICNs attenuates apraxic deficits in AD.

Notably, while all healthy controls scored above the cut-off in the KAS, significant correlations were observed between their praxis scores for pantomime and bucco-facial gestures with the dynamic connectivity between the PMC and left cerebellar ICNs. This finding underscores that praxis relies on complex motor processes and recruits brain regions known for motor planning and coordination (here: PMC and cerebellum). Notably, different connectivity patterns (AD patients: visual and IPL, healthy controls: PMC and cerebellum) were associated with different subtests of the KAS (imitation, pantomime). These findings suggest that different aspects of praxis are associated with specific connectivity patterns in functionally distinct cortical regions.

4.3. Temporal measures of dynamic connectivity

Apraxic AD patients spent significantly more time in the weakly connected, i.e. segregated, than in the strongly connected, i.e. integrated, state and dwelled longer in that state. Moreover, they switched significantly less often between the two states during the resting-state fMRI session. Notably, these temporal measures of dynamic connectivity were associated with apraxic imitation deficits as assessed by the KAS. Our findings reinforce previous reports, demonstrating the added value of dynamic connectivity analyses in characterizing altered connectivity patterns in neuropsychiatric disorders such as AD (Jones et al., 2012). This notion is further supported by the current finding that dynamic connectivity parameters (i.e., the fraction times in state 1 and the dynamic connectivity between the visual and IPL ICNs in state 1), but not static connectivity parameters, could predict apraxic imitation deficits in the current sample of AD patients with apraxia. Previous research suggests that the brain's ability to flexibly switch between brain states to engage with distinct functional networks over time supports memory function, creativity, information processing, and adequate behavior (Li et al., 2017; Tognoli and Kelso, 2014). In line with this, individuals with reduced dynamic variability tend to perform worse in tasks requiring

cognitive flexibility, information processing, and memory function (Hellyer et al., 2015). The specific significant associations of dynamic connectivity measures with apraxic imitation deficits, but not with disturbed pantomime, supports the notion that apraxia comprises distinct motor-cognitive components (Schmidt et al., 2022). It is also consistent with the clinical observation that imitation deficits are the AD patients' most prevalent apraxic deficits (Johnen et al., 2015). Notably, this is the first study analyzing FC in AD patients with apraxia, revealing an association between apraxic deficits, altered static and dynamic FC, and abnormal temporal measures of dynamic connectivity in AD patients with positive biomarkers.

4.4. Dynamic functional segregation and integration

Dynamic functional segregation and integration are measures of brain organization. While dynamic segregation is supposed to indicate the transient retainment of neural information in a functional domain, dynamic integration supposedly denotes the transient interaction of different functional domains for neural information processing. In the current study, AD patients spent significantly more time in the segregated dynamic connectivity state 1, compared to the integrated state 2. They dwelled longer in state 1 without transitioning, compared to healthy participants. Moreover, these temporal dynamic connectivity measures were associated with apraxic imitation deficits, i.e., patients with more severe imitation apraxia had higher fraction and dwell times in the segregated dynamic connectivity state 1. Consistent with this finding, previous studies have suggested that patients with neurological deficits exhibit a preference for segregated states. For example, stroke patients with severe motor deficits were more likely to transition into a segregated state than stroke patients with moderate motor deficits and HC participants (Bonkhoff et al., 2020). The ability to imitate gestures requires the integration and coordination of input from visual and higher-order motor areas. Therefore, the increased time spent in a segregated state may indicate the reduced capacity to dynamically integrate and process visuomotor information, contributing to deficits in gesture imitation. Previous work suggests that increased presence in segregated states of individuals with severe motor deficits may reflect a compensatory mechanism toward reinforcing preserved function within domains (Bonkhoff et al., 2020). Similarly, in this study, the observed preference for a segregated network state in AD patients with apraxia might reflect a shift toward maintaining stable processing within functionally specialized domains at the expense of integration across domains. Thus, this attempt at segregation could be interpreted as a compensatory mechanism to stabilize local functions in the face of global network disruption. In this sense, the increased segregation observed here may serve to preserve basic functions while impairing higher-order actions that depend on large-scale network interaction. Thus, the current results support the notion that a preference for segregated states might be a hallmark of impaired neurological function (Bonkhoff et al., 2021b), particularly for impaired sensory and motor information integration across distributed functional networks.

4.5. Limitations

While our study has several strengths, such as focusing on patients with biomarker-confirmed AD pathology and carefully assessing their cognitive, motor, and praxis functions, some limitations should be noted. We recruited our study population at the University Hospital of Cologne in Germany. The sex distribution within the patient group (with more men than women) does not align with the common understanding that women are more frequently affected by AD pathology. However, recent years have attributed this observation to other factors, such as women's longevity and biological mechanisms (Zhu et al., 2021). Furthermore, the average years of education in our patient cohort exceed those reported in European cohorts (Hönig et al., 2024). Nevertheless, our two groups were matched regarding sex distribution and years of education. The current study population was relatively small, comprising 14 AD patients with apraxia and 14 matched healthy participants. Despite this small sample size, we demonstrated robust and statistically significant group differences in static and dynamic FC. Our findings, along with prior investigations involving similar patient sample sizes (Evangelisti et al., 2023; Fu et al., 2019; Greicius et al., 2004), suggest that even a relatively low number of patients can be sufficient for the analysis of transient changes in FC using resting-state fMRI measurements. Still, future research would benefit from larger cohorts to validate the current findings and to enable the examination of connectivity patterns across a broader range of disease stages. In this regard, the patient sample in this study predominantly exhibited mild (motor and cognitive) deficits. Future studies may include AD patients covering a broader spectrum of deficit severity to examine whether the association of static and dynamic connectivity parameters and apraxic deficits varies with disease stage. Notably, the comprehensive analysis of static and dynamic FC, as performed in the current study, enabled us to detect altered connectivity patterns already in the current sample of AD patients and mild (apraxic) deficits. Cognitive decline, comprehension problems, or spatial dysfunction can affect praxis performance or mimic apraxic symptoms in AD. To address this, we controlled for global cognitive function, language, and visuo-spatial functions in our correlation analyses. Notably, the inclusion of these cognitive variables strengthened the correlations between FC measures and apraxic deficits, underscoring that the observed associations are likely driven by apraxia.

5. Summary

Using resting-state fMRI data, the present study revealed differences in static and dynamic connectivity between apraxic patients with biomarker-confirmed AD pathology and matched healthy participants. In AD patients with apraxia, reduced static and dynamic connectivity between the visual and IPL ICNs was associated with limb apraxia and apraxic imitation deficits, respectively. Moreover, the current AD patients showed significant associations between increased fraction and dwell times in the segregated, weakly connected dynamic connectivity state 1 and more severe apraxic imitation deficits. Notably, the combination of fraction time and connectivity between the visual and IPL ICNs in the segregated dynamic connectivity state 1 correlated with and significantly predicted the variance in imitation scores. The current findings suggest that apraxic deficits in AD are associated with altered FC and highlight the importance of assessing static and especially dynamic functional connectivity in neuropsychiatric patients to elucidate the pathophysiology of complex motor and cognitive deficits. These results provide novel insights into the functional neural mechanisms underlying apraxic deficits in AD. By demonstrating that specific static and dynamic FC parameters are predictive of apraxic impairments, the present study identifies potential clinical indicators of functional disability. Such markers may help improve early clinical detection of apraxia-related limitations in daily life and contribute to developing targeted interventions to preserve patient autonomy and quality of life.

CRediT authorship contribution statement

Taylan D. Kuzu: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elena Brinkmann:** Writing – review & editing, Methodology, Investigation, Data curation. **Anna K. Bonkhoff:** Writing – review & editing, Software, Methodology, Formal analysis. **Veronika Wunderle:** Writing – review & editing, Investigation, Data curation. **Gérard N. Bischof:** Writing – review & editing, Conceptualization. **Kathrin Giehl:** Writing – review & editing, Conceptualization. **Maximilian H.T. Schmieschek:** Writing – review & editing, Methodology, Data curation. **Oezguer A. Onur:** Writing – review & editing, Funding acquisition, Data curation. **Frank Jessen:** Writing – review & editing, Funding acquisition, Data

curation. **Gereon R. Fink:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Alexander Drzezga:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Peter H. Weiss:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

Alexander Drzezga reports research support: Siemens Healthineers, Life Molecular Imaging, GE Healthcare, AVID Radiopharmaceuticals, Sofie, Eisai, Novartis/AAA, Ariceum Therapeutics; speaker honoraria/advisory boards: Siemens Healthineers, Sanofi, GE Healthcare, Biogen, Novo Nordisk, Invicro, Novartis/AAA, Bayer Vital, Lilly, Peer View Institute for Medical Education, International Atomic Energy Agency, Swiss Rockets; stock: Siemens Healthineers, Lantheus Holding, Lilly; trials: participation including PI-roles in industry-sponsored trials e.g. by Novartis Pharma; patents: patent for 18F-JK-PSMA-7 (patent no.: EP3765097A1; date of patent: January 20, 2021). The other authors have declared no competing interests.

Acknowledgements

The Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) funded this study – Project-ID 431549029 – SFB 1451 and Project-ID DR 445/9-1. Gereon R. Fink and Oezguer A. Onur were supported by the Marga and Walter Boll-Foundation.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2025.09.007.

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