Journal of the Neurological Sciences 475 (2025) 123568

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Foreign language learning in older adults modifies the pattern of resting-state activity in the medial prefrontal cortex

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ARTICLE INFO

Keywords:
Foreign language learning
Aging
Medial prefrontal cortex
fMRI
Rehabilitation

ABSTRACT

Background: Foreign language learning (FLL) enhances cognitive functions in older adults, improving memory, attention, and executive functions and potentially delaying cognitive decline. However, the neural mechanisms underlying FLL's benefit on cognition remain unclear, and current methods for studying changes in brain activity are often operator-dependent, potentially missing important effects. This highlights the need for using data-driven techniques.

Methods: Resting-state functional Magnetic Resonance Imaging (rs-fMRI) data from 27 older adults (FLL: $n = 14$; Control: $n = 13$) were analyzed using a voxel-wise, operator-independent approach, known as fractional Fractional Amplitude of Low-Frequency Fluctuations (fALFF), to identify the FLL-induced longitudinal changes in resting-state neocortical activity. Linear regression analyses further explored links between the longitudinal changes in fALFF and behavioral measures.

Results: The between-groups analysis showed that FLL modified the resting-state activity in the medial prefrontal cortex (mPFC), with bilateral increases in the dorsomedial and orbitofrontal regions, overlapping with the medial anterior part of the DMN. A significant correlation was found between the FLL-related changes of fALFF in the mPFC and performance in semantic verbal long-term memory, as assessed by the Babcock Memory Recall Test.

Conclusions: FLL alters cortical neural organization by increasing mPFC activity, a putative compensatory phenomenon that counteracts aging-related cognitive decline.

1. Introduction

Increasing evidence indicates that Foreign Language Learning (FLL) can positively impact the cognitive abilities of older individuals, such as memory, attention, and executive functions. This suggests that FLL may provide a protective effect against cognitive decline and might help postpone the onset of cognitive deterioration associated with conditions such as dementia [1,2]. Recent models indicate that FLL exerts its beneficial effects by enhancing cognitive control — the ability to filter out irrelevant information — but also by strengthening cognitive persistence, i.e., the ability to adapt to changing rules and persist in problem-solving efforts [3]. Cognitive persistence is particularly relevant in the context of multilingualism because multilingual speakers often need to use inhibitory control to suppress competing languages when speaking in a particular language, especially if that language is less dominant. While individuals with low persistence show a significant

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https://doi.org/10.1016/j.jns.2025.123568
Received 5 March 2025; Received in revised form 12 May 2025; Accepted 4 June 2025
Available online 12 June 2025

drop in performance, those with high persistence continue to engage for more extended periods. Indeed, multilingual speakers activate overlapping brain resources for conflict monitoring and language switching [4]. For example, trilingual speakers experience a more significant "switching cost" when transitioning from their second language to their first if the first language was recently used due to the need to reactivate a previously suppressed language.

In past studies, Magnetic Resonance Imaging (MRI) has been employed to assess the structural and functional changes associated with FLL. In particular, resting-state functional MRI (rs-fMRI) provides information about how FLL shapes the brain connectome at rest [5]. Existing research, though limited to a few studies, indicates that FLL in older adults influences resting-state MRI functional connectivity (rs-fMRI) within multiple brain networks, such as the so-called executive control, language [5], and cingulo-opercular network [3]. However, connectivity studies often rely on operator-dependent methods that require pre-selection of regions of interest (ROIs). Such an approach risks missing significant effects and demands precise spatial accuracy. Moreover, the variability in defining ROI boundaries could account for inconsistencies in findings. To address these limitations, data-driven techniques provide a promising alternative by analyzing neural changes directly from functional data, enabling a more thorough and unbiased whole-brain evaluation.

Growing evidence suggests that FLL protocols may benefit the aging brain by targeting neural systems involved in cognitive control and persistence. A central hypothesis of the present study is that the prefrontal cortex (PFC), particularly its medial region (mPFC), may be a primary neural target of FLL interventions. This hypothesis is based on the well-documented involvement of the PFC in bilingual language processing [6], executive functioning [7,8,9,10,11], and sustained cognitive effort [3]. From a mechanistic point of view, the PFC undergoes age-related neuronal changes that negatively affect these cognitive functions. Notably, the medial PFC (mPFC) plays a pivotal role by exerting "top-down" control over cognitive processes and acting as a central hub in the brain networks most affected by aging and dementia [12]. As a key node of the default mode network (DMN)—a system that balances task-positive activity and maintains brain homeostasis [13,14]—the mPFC is particularly vulnerable to age-related disruptions in functional connectivity. These changes, which often precede structural damage like gray matter atrophy, are associated with cognitive decline and may stem from vascular alterations [13,12]. Importantly, the PFC also receives feedback from BDNF-rich subcortical and temporocortical regions [15,16], indicating a potential mechanism through which FLL could influence neuroplasticity. These findings suggest that the PFC, especially the mPFC, represents both a vulnerable and potentially modifiable target of FLL, supporting its emerging role as a non-pharmacological intervention to counteract age-related cognitive decline [12].

To test this hypothesis, we analyzed Blood Oxygenation Level Dependent (BOLD) resting-state fMRI data from a cohort of 27 healthy older adults who participated in either a four-week FLL intervention ($n = 14$) or an active control protocol ($n = 13$). We hypothesized that the FLL group would show a greater longitudinal increase in neural activity, measured via the fractional Amplitude of Low-Frequency Fluctuations (fALFF), compared to the control group, particularly in prefrontal regions. In fact, from a physiological standpoint, fALFF is a proxy for how "active" a brain region is at rest, based on slow, spontaneous fluctuations in the BOLD signal that are thought to reflect underlying neuronal oscillations and synchronization. Higher fALFF values suggest stronger localized spontaneous neural activity, potentially indicating greater engagement or importance of that region in intrinsic processing. Lower fALFF may indicate reduced baseline activity or possible dysfunction. At the cortical level, fALFF was computed using a voxel-wise, data-driven approach [17,18], indirectly measuring regional spontaneous neural activity. fALFF quantifies the relative power of BOLD fluctuations within the low-frequency range (0.01–0.10 Hz) relative to the full frequency spectrum [19]. This method enables whole-brain analyses without the constraints of a priori ROI selection and has been successfully applied in studies evaluating neural changes following cognitive training in both clinical and healthy populations [20,21]. In addition to group comparisons, we conducted a correlational analysis to investigate whether longitudinal changes in fALFF were associated with changes in cognitive performance. Based on prior findings linking increased prefrontal activity to improved neural efficiency and functional integration [13,3], we expected a positive correlation between fALFF increases and cognitive improvements in the FLL group.

2. Materials and methods

This study re-examines data previously published by our group [5], using a different methodological approach in fMRI data processing and incorporating an additional participant into the Control group. The novelty of this research lies in its use of a data-driven approach to identify changes in cortical activity. The study was approved by the Local Ethics Committee (approval number: Prot. Nr. 835, 24-04-2015), and all participants provided written informed consent. All procedures adhered to the ethical guidelines outlined in the Declaration of Helsinki.

2.1. Experimental design

Twenty-seven older adults were randomly assigned to two groups in a 1:1 ratio and completed the study. Thirteen participants were placed in the Control group, while fourteen were assigned to the FLL group. The FLL group participated in a 16-week beginner-level English language course consisting of weekly two-hour sessions. Each week included a 90-min class taught by a native-speaking instructor, with a 15-min break and 30 min of homework. The course focused on building fundamental English skills, such as vocabulary, grammar, and communication for everyday social situations. Participants also explored cultural elements of British and American English, including traditions and customs. Speaking and writing skills were further honed through team projects that provided opportunities for practical language use, in addition to exercises focused on grammar and vocabulary. The curriculum integrated activities designed to boost listening comprehension, pronunciation, and intercultural communication, covering travel, shopping, and family topics. The native-speaking teacher conducted a qualitative assessment at the beginning and end of the course to evaluate participants' progress. The control group did not engage in any formal training but completed the same pre- and post-tests. To ensure consistency, participants in the control group received monthly phone calls to confirm they maintained their usual lifestyle throughout the 4-month study period. Comprehensive details regarding the study design, participants' clinical histories, and inclusion/exclusion criteria have been previously published [5].

2.2. Neuropsychological investigation

All participants underwent a neuropsychological assessment before and after the FLL intervention. This battery of tests evaluated various cognitive domains, including executive functions, working memory, episodic memory, and fluid intelligence. A thorough neuropsychological evaluation was conducted at baseline and following the 4-month intervention to assess the effects of FLL on multiple cognitive abilities. Cognitive decline was measured using the Mini-Mental State Examination (MMSE). Participants completed the Trail Making Test (TMT) A to assess sustained spatial attention, TMT B for divided spatial attention, and TMT B-A for cognitive flexibility. The Verbal Fluency Test evaluated access to the phonological lexicon and served as an indicator of executive functioning. Immediate and delayed verbal recall was assessed using the Babcock Memory Test. Executive functions were measured using the Frontal Assessment Battery (FAB). The two study groups' complete demographic and neuropsychological profiles are detailed in

our previously published study [5]. In this work, we re-analyzed the behavioral test results using a method previously established by other research groups [22,23,24]. Specifically, raw scores from each neuropsychological test were converted into age-corrected z-scores based on each measure's means and standard deviations of a normative reference group.

2.3. MRI data collection

Subjects underwent MRI scans before (T_1) and after (T_2) the FLL intervention. Imaging was conducted using a Philips Achieva 3 Tesla scanner (Philips Medical Systems, Best, Netherlands). Anatomical images were acquired with a 3D fast field echo T1-weighted sequence (dimensions: 170 × 240 × 240 mm^3, slice thickness = 1 mm, in-plane voxel size = 1 × 1 mm). T1 images were utilized in the preprocessing of BOLD rs-fMR images to generate gray/white matter and cerebrospinal fluid (CSF) masks, which were used for confounding removal. For each scan, BOLD rs-fMRI images were collected with eyes closed using a gradient-echo T2*-weighted echo-planar sequence (FLL group: 3 runs; dimensions: 80 × 80 × 35 × 180; FOV 240 mm; TR = 1.8 s, voxel size: 3 × 3 × 3 mm^3; control group: 4 runs; dimensions: 64 × 64 × 30 × 145; FOV = 256 mm; TR = 1.67 s; voxel size: 4 × 4 × 4 mm^3). The total acquisition time of the rs-fMRI sessions is 972 s for the FLL group and 968 s for the HC group.

2.4. Rs-fMRI data analysis

The data were processed using the Conn toolbox (version 22; https://web.conn-toolbox.org), following a standard preprocessing pipeline with default settings as described by Whitfield-Gabrieli and Nieto-Castanon [25]. The preprocessing of the functional images began with motion correction using the "realign & unwarp" algorithm in SPM, which aligns each scan to a reference volume through a rigid-body transformation based on a least-squares approach. To correct temporal discrepancies between slices caused by the sequential nature of fMRI acquisition, slice-timing correction was applied using the SPM12 implementation. Outlier volumes affected by excessive motion or signal deviations were identified using the ART toolbox based on framewise displacement and global signal intensity thresholds. Anatomical and functional images were normalized to MNI space, segmented into gray matter, white matter, and cerebrospinal fluid (CSF), and resampled to a voxel size of 2 mm^3. No spatial smoothing was applied. A denoising step followed, using Conn's default approach to remove nuisance variables. Noise from white matter and CSF was estimated based on signals extracted from anatomically defined masks created through binary erosion of posterior probability maps. From each noise region of interest (ROI), five components were extracted: the average BOLD signal and the first four principal components obtained via PCA. Additionally, twelve motion-related regressors, corresponding to six realignment parameters (three translations and three rotations) and their first derivatives, were included to account for motion-induced artifacts. The preprocessed BOLD time series underwent band-pass filtering (0.008–0.09 Hz) to retain low-frequency fluctuations of interest. A CompCor-based strategy was used to further correct for physiological and movement-related noise by extracting orthogonal principal components from white matter and CSF masks, combined with motion regressors and outlier flags. The rs-fMRI data were analyzed using the fALFF method, a fully data-driven, voxel-wise approach [19]. fALFF maps offer a relative measure of BOLD signal power within a specific frequency band of interest (typically 0.01–0.1 Hz) compared to the power across the entire frequency spectrum. fALFF is calculated as the ratio of the root mean square of the BOLD signal at each voxel after band-pass or low-pass filtering, relative to the signal before filtering [19].

2.5. Statistical analysis

For each voxel, independent General Linear Model (GLM) estimation was performed, with the first-level fALFF measure between post-treatment (T_2) and pre-treatment (T_1) conditions, serving as the dependent variable. The two groups (FLL and Control) were treated as independent variables, with age included as a nuisance factor. Hypotheses at the voxel level were tested using multivariate parametric statistics, accounting for random effects across subjects and sample covariance across multiple measures. Cluster-level inferences (for contiguous groups of voxels) were derived using Gaussian Random Field theory [26]. Results were thresholded with a combination of a voxel-level cluster-forming threshold of $p < 0.001$ and a false discovery rate (FDR)-corrected cluster-size threshold of $p < 0.05$ [27]. Finally, within the FLL group, stepwise linear regressions were conducted to examine the association between changes (difference across the two time points, T_2-T_1) in fALFF and the scores on neuropsychological assessments, selectively for those tests that showed a significant effect of the intervention (MMSE and Babcock Memory Test).

3. Results

3.1. Resting-state functional changes related to FLL

The between-groups analysis, which compared the longitudinal changes in the FLL and Control groups, revealed fALFF variations in two cortical clusters of the PFC (Fig. 1; Table 1). Specifically, the FLL group exhibited bilateral increases in fALFF extending across the dorsomedial and orbitofrontal regions of the mPFC, which, according to Yeo's Atlas [28], overlap with the medial anterior portion of the DMN.

The within-group analysis, comparing the longitudinal changes within the FLL group (T_2 vs. T_1), also confirmed the increase in fALFF in the mPFC (**Suppl. Fig. 1**). In contrast, the control group showed no significant changes in cortical activity.

3.2. Relationships between the rs-fMRI and neuropsychological outcomes

FLL significantly influenced the MMSE score ($p < 0.001$) and the Babcock Memory Recall Test ($p = 0.009$). A significant correlation was found between the fALFF strength in the mPFC cluster and performance in semantic verbal long-term memory, as assessed by the Babcock Memory Recall Test ($\beta = 0.848$, $t = 2.949$, $p = 0.012$; Fig. 1; **Suppl. Table 1**). No significant correlation was found between the fALFF strength in the mPFC and MMSE scores (**Suppl. Table 2**).

The within-group analysis also showed that, in the control group, no significant relationship was found between the fALFF strength in the mPFC cluster and the Babcock Memory Recall Test (**Suppl. Fig. 2**).

4. Discussion

The present study employed a voxel-wise, operator-independent approach to identify changes in rs-fMRI cortical activity induced by an FLL program in older adults. Notably, FLL intervention elicited increased resting-state activity in two regions of the mPFC, and this change in brain activity was positively correlated with the longitudinal improvement in delayed verbal memory.

From a methodological point of view, fALFF is a metric that enables the exploration of neuronal activity at the cortical level by analyzing the power of the BOLD signal within a specific frequency window. This method is advantageous as it provides a direct measure of neuronal activity, mapping brain dynamics on a voxel-by-voxel basis. The voxel-wise approach allows for whole-brain exploration without predefining regions of interest, reducing the risk of bias and increasing sensitivity in detecting local changes in cortical areas. Essentially, fALFF helps us better understand how cortical activity, particularly in areas related to executive control and language, can be influenced by FLL. While the use

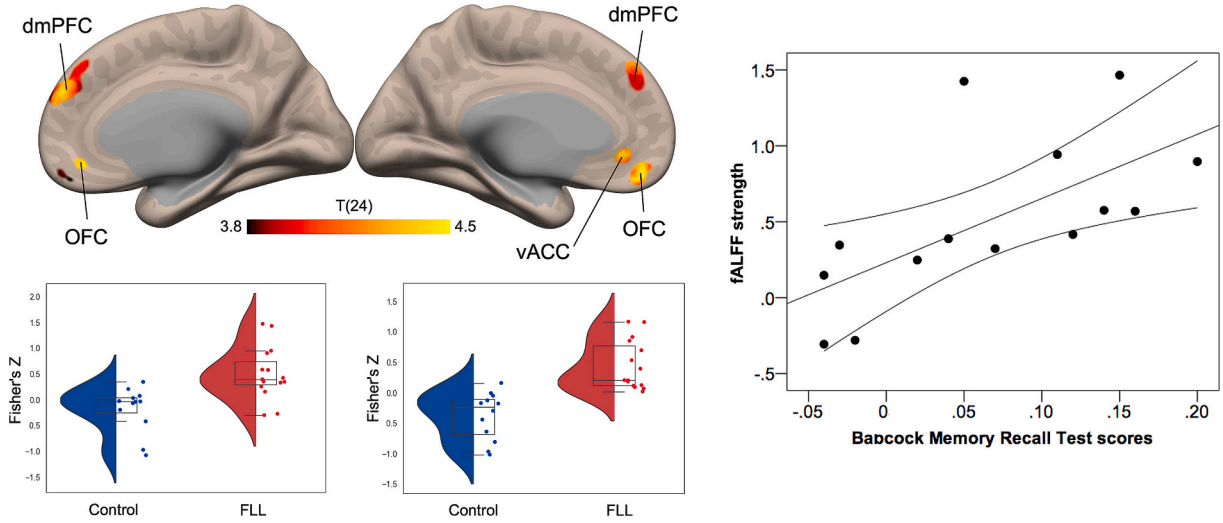

Fig. 1. Resting-state activity changes associated with FLL intervention. The left panel illustrates the between-group differences in fALFF. The map highlights bilateral clusters in the dorsomedial prefrontal cortex (dmPFC), ventroanterior cingulate cortex (vACC), and orbitofrontal cortex (OFC) regions of the medial prefrontal cortex (mPFC), where intrinsic activity is significantly increased (yellow cluster) in the FLL group compared to the Control group. The plots display individual and group distributions of rs-FC metrics for each group and cluster. The box represents the quartiles of the dataset. At the same time, the whiskers extend to show the rest of the distribution, expressed as multiples (by default, 1.5) of the inter-quartile range (IQR), which is the range between the lower and upper quartiles covered by the inner box. The IQR function identifies observations that fall outside this range as potential outliers, which are then shown outside the whiskers. The right panel presents a scatterplot demonstrating the correlation between the fALFF values in the dmPFC and the Babcock Memory Recall Test scores among FLL subjects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Significant clusters obtained from fALFF analysis and their characteristics/location.

Cluster	Coordinates (MNI: X,Y,Z)	size (mm^2)	size p-FWE	size p-FDR	size p-uncorr	peak p-FWE	peak p-unc
dmPFC	+4, +58, +26	129	0.00229	0.00347	0.00005	0.99347	0.00005
OFC	0, +44, −10	102	0.00962	0.00731	0.00021	0.88260	0.00002

Abbreviations: dmPFC = dorsomedial PreFrontal Cortex; OFC=OrbitoFrontal Cortex.

of fALFF in the context of FLL interventions is still relatively limited, converging evidence from other resting-state and task-based studies suggests that second language acquisition can modulate the activity and functional organization of prefrontal regions. One study using functional Near-Infrared Spectroscopy found that individuals with higher foreign language proficiency showed elevated prefrontal activation even during native language use, suggesting sustained frontal engagement potentially linked to language control and inhibition mechanisms [29]. Another fMRI study showed that the acquisition of new vocabulary in a non-native language recruited overlapping networks with the native language but evoked stronger prefrontal activation when processing the native language, likely due to increased lexical competition [30]. Similarly, network-based approaches have demonstrated that language learners show increased integration between prefrontal, parietal, and temporal regions, with successful learners engaging more distributed frontal networks associated with memory and executive control [31]. This remodeling of functional architecture has been interpreted as a marker of brain plasticity that supports linguistic and domain-general cognitive functions [31]. These findings suggest language learning in older adulthood may enhance prefrontal dynamics and support compensatory mechanisms to counteract age-related cognitive decline. This interpretation aligns with the Scaffolding Theory of Aging and Cognition (STAC), which posits that increased activation in frontal regions may reflect compensatory mechanisms in response to age-related decline [32].

Consistent with our working hypothesis, we observed increased activity in the mPFC in subjects who participated in the FLL program. The mPFC plays a fundamental role in numerous cognitive processes, including memory, motivation, decision-making, and behavioral adaptation, acting as an integrative hub that coordinates information from various brain regions [33,30,34]. One of the key functions of the mPFC is to provide semantic schemas for storing and retrieving information [35,33,34]. Once the information has been acquired, the mPFC supports its long-term storage into existing schema, aiding the learning and retention of new knowledge [36]. However, aging has been shown to lead to structural and functional alterations in the mPFC that compromise many of its cognitive abilities. Specifically, neuroanatomical studies have revealed a reduction in volume and gray matter in the mPFC with age, which contributes to the decline of cognitive functions such as working memory, cognitive flexibility, and attention [37]. The decreased connectivity between the mPFC and other cortical and subcortical areas is a hallmark of age-related cognitive decline [38,39]. Furthermore, the mPFC is one of the first targets of neurodegenerative diseases: in Alzheimer's disease, for instance, the progressive atrophy of the mPFC, along with the accumulation of beta-amyloid plaques, severely impairs executive functions and working memory [12]. Similarly, in Parkinson's disease, the loss of dopamine and damage to cortical circuits, including the mPFC, contribute to the deterioration of decision-making, working memory, and planning abilities [12].

We speculate that the increase in mPFC activity observed in the subjects who participated in the FLL program may reflect a compensatory mechanism aimed at counteracting the neural effects of cognitive decline associated with aging. This is consistent with the observed significant correlation between the changes in fALFF in the mPFC and improvements in semantic long-term memory, as assessed by the Babcock Memory Recall Test. In particular, the observed increase in mPFC

activity could reflect an adaptive response, where the mPFC recruits additional cognitive resources to support the incorporation of new semantic information into existing schema despite age-related structural and functional alterations. This suggests that the FLL program may stimulate the mPFC to restore or enhance its role in memory processing, aiding the retention and retrieval of new knowledge. Following this hypothesis, the relationship between fALFF changes and memory improvements may not simply represent a correlation but may indicate that the FLL program activates a compensatory response in the mPFC that helps preserve cognitive function in the face of aging. This adaptive mechanism could mitigate the effects of the age-related decline in neural efficiency and connectivity within this key brain region, helping to sustain memory performance over time. This interpretation aligns with the Scaffolding Theory of Aging and Cognition (STAC), which posits that increased activation in frontal regions may reflect compensatory mechanisms in response to age-related decline [32].

The present study has some limitations. First, although FLL significantly improved MMSE scores - a commonly used but basic tool for evaluating overall cognitive decline - it did not show notable effects on specific cognitive areas, apart from enhancements in long-term verbal memory measured by the Babcock Story Recall Test. This indicates that FLL may offer general cognitive advantages, but its effects on individual cognitive skills could be subtler or require more precise assessments. Second, we acknowledge that this study is exploratory, a pilot investigation with a relatively small sample size. The limited sample size may reduce the statistical power to detect subtle effects of FLL on cognitive performance across different domains and may limit the generalizability of the findings. Expanding the sample size in future studies would allow for a more robust analysis, potentially uncovering effects that were not evident in the current study. Third, the study's design did not include a long-term follow-up to assess the durability of the observed cognitive benefits. It remains unclear whether the improvements in long-term verbal memory persist over time or diminish without continued intervention. Longitudinal studies are needed to determine the sustainability of the cognitive effects induced by FLL. Fourth, individual factors, such as language proficiency, age of language acquisition, and personal motivation, could influence the benefits observed from the FLL program. In particular, more experienced bilingual individuals or those with higher intrinsic motivation may experience more pronounced cognitive improvements. Future research could explore how these variables affect the effectiveness of the program. Lastly, although FLL shows promising results, it would be interesting to compare it with other cognitive intervention methods, such as cognitive stimulation or dedicated multiple language training programs. This comparison could help better understand the specific advantages of FLL compared to different approaches and identify potential synergies. Finally, we recognize that the resting-state fMRI data for the FLL and control groups were collected using slightly different protocols. To minimize potential issues related to data comparability, all functional data were processed with the same pipeline (CONN toolbox), including spatial normalization to MNI space and resampling to a uniform voxel size ($2 \times 2 \times 2$ mm). Given that brain connectivity measures rely on correlations over extended time periods, we believe that the small TR variation (0.13 s) is unlikely to significantly affect the accuracy of the connectivity analyses. Indeed, the retained frequencies of interest for resting state connectivity in our analysis (and according with the literature) are in the range 0.008–0.09 Hz, which are adequately sampled with both TRs considering the Nyquist theorem.

5. Conclusions

In summary, our study provides preliminary evidence that a structured FFL program can induce beneficial neural changes in older adults by increasing resting-state activity in key regions of the medial prefrontal cortex. These neural changes were accompanied by improvements in semantic long-term memory, suggesting that FLL may offer a promising non-pharmacological intervention to mitigate age-related cognitive decline. Although the pilot nature of this study and its modest sample size warrant cautious interpretation, the findings lay the necessary groundwork for future research. Subsequent studies with larger cohorts and extended follow-up periods are needed to further validate these results and explore the long-term sustainability of the cognitive benefits associated with FLL. Overall, our work underscores the potential of engaging cognitive interventions to harness neural plasticity, ultimately contributing to the development of effective strategies for healthy cognitive aging.

CRediT authorship contribution statement

Giovanna Bubbico: Writing – original draft, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Federica Tomaiuolo:** Formal analysis, Data curation. **Carlo Sestieri:** Writing – original draft, Conceptualization. **Golnoush Akhlaghipour:** Writing – review & editing. **Alberto Granzotto:** Writing – review & editing. **Giovanni Martinotti:** Writing – review & editing. **Antonio Ferretti:** Writing – review & editing. **Mauro Gianni Perrucci:** Writing – review & editing, Resources. **Stefano L. Sensi:** Writing – review & editing, Supervision. **Stefano Delli Pizzi:** Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

AF and SLS acknowledge financial support from Strengthening of Research Structures and creation of R&D "Innovation Ecosystems," National Recovery and Resilience Plan (NRRP), Mission 4, Component 2 Investment 1.5, funded from the European Union–NextGenerationEU–VITALITY, ECS00000041 (grant no. D73C22000840006). GB acknowledges partial funding from the project Departments of Excellence of the Italian Ministry of Education, University and Research (MIUR). This work was also partially supported by the Departments of Excellence 2018–2022 initiative of the Italian Ministry of Education, University, and Research for the Department of Neuroscience, Imaging, and Clinical Sciences (DNISC) of the University of Chieti–Pescara, and the NRRP - Mission 4 "Education and Research" - Component 2 "From Research to Business" - Investment 1.2 "Funding projects presented by young researchers – Seal of Excellence", Next Generation EU SOE_0000062 CUP D73C22001930006.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2025.123568.

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