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Age-related prefrontal cortex activation in associative memory: An fNIRS pilot study

Deborah Talamonti^{a,b,*}, Catharine A. Montgomery^b, Dan P.A. Clark^c, Davide Bruno^b

^a EPIC Center, Montreal Heart Institute, Montreal, Quebec, Canada

^b School of Psychology, Liverpool John Moores University, Liverpool, United Kingdom

^c Department of Psychology, Liverpool Hope University, Liverpool, United Kingdom

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ABSTRACT

Older adults typically perform more poorly than younger adults in free recall memory tests. This age-related deficit has been linked to decline of brain activation and brain prefrontal lateralization, which may be the result of compensatory mechanisms. In the present pilot study, we investigated the effect of age on prefrontal cortex (PFC) activation during performance of a task that requires memory associations (temporal vs. spatial clustering), using functional Near-Infrared Spectroscopy (fNIRS). Ten younger adults, ten cognitively high-performing older individuals, and ten low-performing older individuals completed a free recall task, where either a temporal or spatial strategy (but not both simultaneously) could be employed to retrieve groups of same-category stimuli, whilst changes in PFC hemodynamics were recorded by means of a 12-channel fNIRS system. The results suggest PFC activation, and right lateralization specific to younger adults. Moreover, age did not affect use of memory organization, given that temporal clustering was preferred over spatial clustering in all groups. These findings are in line with previous literature on the aging brain and on temporal organization of memory. Our results also suggest that the PFC may be specifically involved in memory for temporal associations. Future research may consider whether age-related deficits in temporal organization may be an early sign of PFC pathology and possible neurodegeneration.

1. Introduction

An unavoidable consequence of older adulthood is age-related brain decline, which manifests with gradual loss of hemispheric specialization (Cabeza et al., 1997), amongst other symptoms, such as changes in cerebral blood flow and loss of volume of brain tissues (Agbangla et al., 2017; Bertsch et al., 2009; Jernigan et al., 2001; Pakkenberg et al., 2003). The Hemispheric Asymmetry Reduction in Older adults (HAROLD) model (Cabeza, 2002) postulates that reduced lateralization, particularly in the prefrontal cortex (PFC), yields activation of bilateral or opposite areas to those typically utilized in younger adulthood, probably as attempt to counteract the age-associated neurocognitive decline. Furthermore, the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) model (Reuter-Lorenz and Cappell, 2008) suggests that these compensatory mechanisms allow older adults to achieve an equal level of performance as their younger peers in low demanding tasks, but not in high demanding tasks, where the compensation strategy may fail to overcome the age-related brain decline. A typical pattern shown in younger adults, for example, im-

plicates activation of the left PFC during learning of new memories (encoding), whilst retrieval causes activation of the right PFC. These observations have been found with both verbal and non-verbal information (Habib et al., 2003) and are described in the Hemispheric Encoding/Retrieval Asymmetry (HERA) model (Tulving et al., 1994). Older individuals, however, show opposite (Cabeza et al., 1997) or bilateral (Cabeza et al., 2002) patterns, whilst performing similarly to younger adults, consistent with the HAROLD and CRUNCH models. These age-related cerebral changes are related to deficits in a variety of cognitive functions, including episodic memory (Cabeza et al., 2017). However, in the domain of human memory, several phenomena have been explained from a cognitive approach, but still need neuroscientific corroboration. For instance, cognitive studies on episodic memory suggest that age-related memory deficits may be the result of a decreased ability to form associations between items at recall, known as the associative-deficit hypothesis (Naveh-Benjamin, 2000). Temporal contiguity is a form of associative process that permits organization of memories following the temporal order in which events are perceived (Kahana, 1996). Evidence of temporal contiguity is consistently

* Corresponding author at: EPIC Center of the Montreal Heart Institute, 5055 Rue Saint-Zotique E, Montreal, Quebec H1T 1N6, Canada.

E-mail addresses: deborah.talamonti@umontreal.ca (D. Talamonti), C.A.Montgomery@ljmu.ac.uk (C.A. Montgomery), clarkd@hope.ac.uk (D.P.A. Clark), d.bruno@ljmu.ac.uk (D. Bruno).

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reported in laboratory tasks and is particularly evident in studies of younger adults (Healey and Kahana, 2014). Although some studies have investigated temporal contiguity in association with activity of the temporal lobe (Bruno et al., 2016; Manning et al., 2011), activation of the PFC has been observed during recall of memory for temporal context (Amiez and Petrides, 2007; Jenkins and Ranganath, 2010) in younger individuals.

Memory for temporal order appears to be particularly challenging in older adults (Craik and Salthouse, 2016; Parkin et al., 1995), and is impaired in individuals with Mild Cognitive Impairment (MCI) (Gillis et al., 2013). Golomb et al. (2008) also observed that, whilst temporal associations were not employed efficiently, older adults tended to retrieve items clustered by semantic category, even when maladaptive for serial recall. These findings suggest that older adults engage alternative associative processes in order to overcome the age-related deficiency in temporal clustering. Given that semantic contiguity has been found persistently in older adults (Healey and Kahana, 2016) and at the cost of efficient memory performance (Golomb et al., 2008), it is possible that other forms of memory organization may be preferred by older adults, as a compensatory cognitive strategy similar to what suggested by CRUNCH. For instance, when spatial attributes are provided to younger adults, these attributes have been found to influence the output order of recall by increasing spatial contiguity (Miller et al., 2013). Involvement of the hippocampus and the PFC have been reported during retrieval of spatial context in younger adults (Burgess et al., 2001; Hayes et al., 2004; Maguire et al., 1997), thus suggesting that similar areas may be activated during spatial clustering. Although age-related deficits for spatial memory have been previously reported (Old and Naveh-Benjamin, 2008), the current literature suggests that this age-related decline becomes evident only in complex tasks, most probably as consequence of attentional/executive deficits (for a review see: Klencklen et al., 2012). For instance, Pouliot and Gagnon (2005) showed that, although significantly different, older participants experienced only a minor decrease on recall for spatial locations compared to the younger group. Olson et al. (2004) found that younger and older adults showed similar performance on the short-term spatial memory test and that both groups encoded locations relative to other locations. Taken together, these studies suggest that in older adults experiencing deficits in temporal clustering, spatial contiguity may be an efficient alternative form of memory organization.

To the authors' knowledge, no study has explored the brain areas specifically involved during spontaneous spatial versus temporal associations in different age groups. It is therefore critical to explore both neural and cognitive substrates of temporal and spatial contiguity in order to understand better how age and cognitive status affects these processes.

The present study is the first to investigate age-related changes in functional PFC patterns during associative processes and age-related differences in the use of temporal vs. spatial clustering in younger adults and in cognitively high- vs. low-performing older participants. Moreover, this was the first study to explore these processes and patterns using functional Near-Infrared Spectroscopy (fNIRS). fNIRS is a non-invasive functional brain imaging technique that detects hemodynamic changes in the human cortex (for a review see: Ferrari and Quaresima, 2012), similar to functional Magnetic Resonance Imaging (fMRI). Based on the optical absorption properties of blood hemoglobin, fNIRS enables calculation of concentration changes in oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HHb), which are indicators of cortical activation (Jöbsis, 1977). Compared to the fMRI, fNIRS provides better temporal resolution, is relatively insensitive to motion artefacts, user-friendly and potentially portable. These aspects make fNIRS a particularly useful technique in studies with older adults and individuals with dementia (Arenth et al., 2007; Li et al., 2018). Although providing lower spatial resolution and penetration depth compared to fMRI, and causing disadvantages related, but not limited, to skin response and skull thickness (Ferrari and Quaresima, 2012), the utility of fNIRS in

exploring cortical activation of the PFC in response to cognitive tasks has been repeatedly shown (Holtzer et al., 2018).

Consistent with previous research presented above, it was hypothesized that: (1) following the HAROLD and CRUNCH models, younger adults would show greater lateralized PFC activation during associative memory, compared to the older groups, and (2) older individuals with lower cognitive functioning would employ greater spatial clustering, compared to younger adults, as an alternative to temporal clustering.

2. Material and methods

2.1. Participants

Thirty individuals were selected for the study. Ten participants were university students ($M = 28.60$; $SD = 3.24$; age range = 23–33). Twenty individuals were from the University of Third Age, aged 60 or above ($M = 69.55$; $SD = 5.11$). Of these, ten ($M = 68.10$; $SD = 5.59$; age range = 60–75) were classified as cognitively high-performing and ten ($M = 71.00$; $SD = 4.40$; age range = 65–77) as cognitively low-performing on the basis of performance in the neuropsychological screening (details in the Procedure section). Participants were selected if they reported no current or past diagnosis of neurological diseases, psychiatric conditions and diagnosed neurodegenerative disorders. Participants were required to be fluent in English and right-handed. All participants were also matched by sex. The study was approved by the University's Research Ethics Committee and completed in accordance with the Declaration of Helsinki.

2.2. Procedure

All participants provided informed consent. Older adults firstly undertook the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), a 20-minute neuropsychological battery used in clinical practice to investigate cognitive functioning, in order to exclude those with undiagnosed cognitive decline or dementia. The RBANS includes 12 subtests, administered and scored as described in the manual, measuring attention (digit span, coding), language (picture naming, semantic fluency), visuospatial and constructional abilities (figure copy, line orientation), and immediate and delayed memory (list learning, recognition and recall, story memory, figure recall). The 12 subtests yield 5 Index scores and a Total Scale score. Average RBANS scores range from 90 to 109, whereas scores between 80 and 89 are considered low average cognitive performance. Low-performers and high-performers were identified based on a cut-off of 90, the lower average score (Randolph, 1998). Although significantly different on the RBANS total score, the resulting two groups did not statistically differ in age or total years of education (calculated from the first year of primary school to the last year of formal education), as shown in Table 1. Following the administration of the RBANS, older adults completed the memory test (see next section), simultaneously to fNIRS recording. Given the exclusion criteria of the study, younger participants were excluded from the neuropsychological screening, which is specific to detect cognitive decline in older adults or in individuals with neuropsychiatric conditions, and only completed the memory test and the fNIRS recording. According to the length of each experimental condition, older participants were reimbursed with a £15 voucher, whilst younger participants were given £10 voucher as compensation. Data is available on an Open Access basis through the Liverpool John Moores University Research Data Repository, at: <https://doi.org/10.24377/LJMU.d.00000079>.

2.2.1. Memory assessment

Memory performance was assessed in all participants using the Spatial-Temporal Memory test (STeM). The STeM is a ten-minute test including four picture naming trials, each of which followed by free recall. Stimuli were selected from Moreno-Martínez and Montoro (2012),

Table 1
Demographics and comparisons of cognitive functioning in younger adults and in low-/high-performing older participants.

| | Younger (n = 10) | High-performers (n = 10) | Low-performers (n = 10) | p |
|---------------------------|------------------|--------------------------|-------------------------|--------|
| Age (years) | 28.60 ± 3.24 | 68.10 ± 5.59 | 71.00 ± 4.40 | .213 |
| Females (%) | 5 (50%) | 5 (50%) | 5 (50%) | – |
| Years of formal education | 20.30 ± 2.00 | 14.15 ± 2.98 | 13.10 ± 2.28 | .388 |
| RBANS | – | 101.00 ± 2.21 | 86.00 ± 2.98 | <0.001 |
| STeM Total score | 28.10 ± 2.06 | 28.10 ± 2.06 | 27.60 ± 0.69 | .322 |
| STeM temporal contiguity | 0.56 ± 0.07 | 0.58 ± 0.09 | 0.53 ± 0.09 | .300 |
| STeM spatial contiguity | 0.50 ± 0.09 | 0.49 ± 0.09 | 0.48 ± 0.09 | .720 |

Note. Data are mean ± standard deviation; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; STeM = Spatial-Temporal Memory test; p = group differences between cognitively high-performing and low-performing older adults.

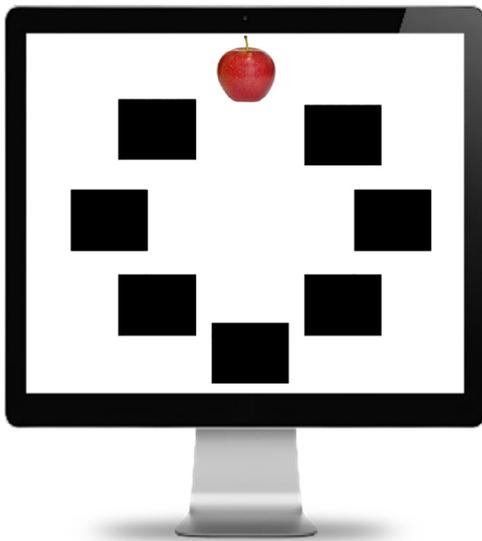


Fig. 1. An example of the STeM test.

and were presented in colors on a white background, using E-Prime 2.0 software (Psychology Software Tools, PA, USA). Each trial involved presentation of eight stimuli belonging to the same category, for a total of thirty-two stimuli. In trial one, eight images of fruits were encoded and recalled; in trial two, three and four of those images were replaced respectively by eight images of vegetables, eight of items of clothing, and eight of animals. Stimuli were semantically related (within each block, but not across blocks) in order to avoid unexpected semantic interference during the retrieval phases, and to force the use of temporal or spatial clustering exclusively. Each item from the same category appeared on the computer screen, positioned 30 cm from participants, for 3000 ms, with a 1000 ms inter stimulus interval, in a circular array containing seven black boxes and a target picture (see Fig. 1). All items were displayed randomly, so that any picture could appear in any of the boxes and in any temporal order.

During the study phase participants were introduced to the memory task and instructed to name each image with the following instructions: “We are going to show you a series of boxes arranged around a circle. One of the boxes will be replaced by a picture of a well-known [category name]. Your task is to look at the picture and to name the item. The image will be displayed for 3 s and then the next image will load”. Naming the items ensured participants were attending to, and accurately perceiving, each stimulus. After each category was presented, participants were asked to verbally recall the presented items in any order, before proceeding to the next category of images. Recall was free, therefore its duration varied amongst participants, although generally it was completed within ten seconds. The output order of recall was examined to calculate memory performance (STeM total recall), spatial

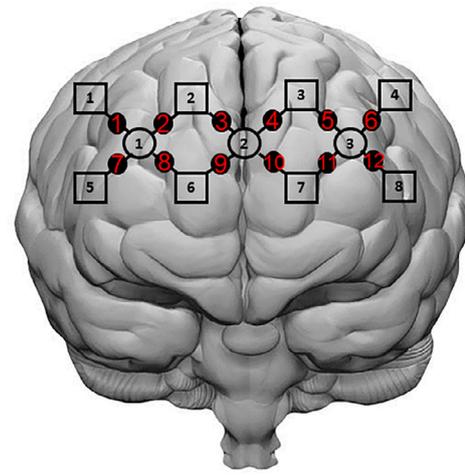


Fig. 2. Approximate 12-channels configuration of the fNIRS.

(STeM-S) and temporal (STeM-T) clustering (details on the calculations in the Data analysis section).

2.3. fNIRS instrumentation and signal processing

For the entire duration of the memory test, the hemodynamic response was recorded, preceded by a 2-minute baseline recording, during which participants were asked to relax while listening to music and looking at pictures of landscapes on the computer screen. The baseline recording period was used to calculate changes in the hemodynamic response, as detailed below. During the STeM, changes in HbO and HHb were monitored using a 12-channel continuous wave fNIRS device (OxyMon MK III, Artinis Medical System TM, The Netherlands). In all STeM tasks, an event-related design was used and the inter-trial interval was of 10 s prior and after the recall of blocks. The short delay was included in order to ensure that participants’ acute hemodynamic response had dissipated before the next task started. Sample frequency was set at 10 Hz (Basso Moro, Cutini, Ursini, Ferrari, and Quaresima, 2013; Ferreri et al., 2014; Metzger et al., 2016). Changes in light attenuation were measured at two wavelengths (765 and 855 nm) and using the modified Beer-Lambert law. As part of this calculation, the age-dependent differential path-length factor (DPF) was given by the formula: $4.99 + 0.067 \times (\text{Age}^{0.184})$ in young adults (Duncan et al., 1996). Data on variation of DPF in adults aged 50 or above is not currently available, thus, DPF in the older group was set to 6.61 corresponding to age 50, in accordance with previous literature (Claassen et al., 2006; Vermeij et al., 2012).

Three sources and eight detectors were positioned, on an adjustable EEG cap, symmetrically over the bilateral PFC, according to the international EEG 10–20 system (Jasper, 1958) (see Fig. 2). When needed, hair was removed from the optical fibers to reduce extra-cranial light loss

and signal quality was verified before and during the entire measurement, with HbO, HHb and total hemoglobin (tHb) displayed in real time. The source-detector separation of 2.5 cm allowed for 1.25 cm penetration depth (Haeussinger et al., 2011). The investigated cerebral areas were: dorsolateral PFC, anterior PFC and medial PFC, corresponding to Brodmann areas (BAs) 46, 10 and 9. Data were pre-processed according to the modified Beer–Lambert law logarithm in the OxySoft software (Artinis Medical System TM, the Netherlands). Data were visually inspected. A 2-s moving-gaussian filter was applied to attenuate the noise due to respiration and heart beat frequency. All measurements were relative changes in concentration of HbO and HHb, compared to baseline, since continuous-wave NIRS devices do not allow to determine absolute concentration of HbO and HHb. Specifically, to determine the changes in the hemodynamic response during associative processes, data were baseline-corrected using the mean value of the baseline period. Then, channels were grouped together for analysis, for comparison of regions of the PFC. Channels 1 and 7 were grouped together as the right DLPFC region (BA46). Channels 6 and 12 were grouped together as the left dorsolateral prefrontal cortical (DLPFC) region, corresponding to BA46. 2 and 3, and 4 and 5 corresponded to the right and left medial PFC (BA9), respectively. Channels 8 and 9, and 10 and 11 corresponded to the right and left anterior PFC region (BA10). Finally, HbO and HHb changes from baseline were averaged over the four SteM recall epochs. Following this procedure, which included averaging the hemodynamic response over channels and consequentially over trials, allowed to maintain the variance over sessions (Spüler, 2019).

2.4. Statistical analysis

Statistical analyses were performed using SPSS, Version 23 (IBM) and all assumptions were met to perform the following analyses. For behavioral results, an independent-samples *t*-test was run to identify older adults who were high- and low- performing, given the RBANS total score. A univariate ANOVA was conducted to analyze group differences on SteM total recall. SteM clustering scores were calculated adopting the method developed by Polyn et al. (2009). Specifically, the absolute value of the lag of each recall transition was ranked with the absolute values of the lags of all possible transitions. This provided a percentile score for each transition, which was then averaged with the other percentile scores of a participant's transitions, therefore providing a temporal factor score. Since these scores can be confounded by several factors including unexpected semantic clustering, values were then corrected by chance using the procedure defined by Healey (2018), where a permutation distribution was created by randomly shuffling the order of recall within the sequence 10,000 times and computing a temporal score for each shuffle. The actual temporal factor score was then converted into a z-score by subtracting the permutation's mean and dividing by its standard deviation. The same analysis was run to compute the spatial clustering score. Therefore, a 3 (group: younger, low-performers, high-performers) \times 2 (clustering: spatial, temporal) mixed ANOVA was used to test significant age-related differences in use of temporal or spatial clustering.

For fNIRS data, group differences in HbO and HHb concentrations were analyzed using a 2 (location: left, right hemisphere) \times 3 (group: younger, low-performers, high-performers) \times 3 (BA: 46, 10, 9) mixed ANOVA.

3. Results

3.1. Behavioral data

Descriptive statistics for demographic data of all groups are reported in Table 1, along with *t*-tests, where differences on general cognitive functioning between low- and high-performing older adults are reported. Data are mean \pm standard deviation, unless otherwise stated.

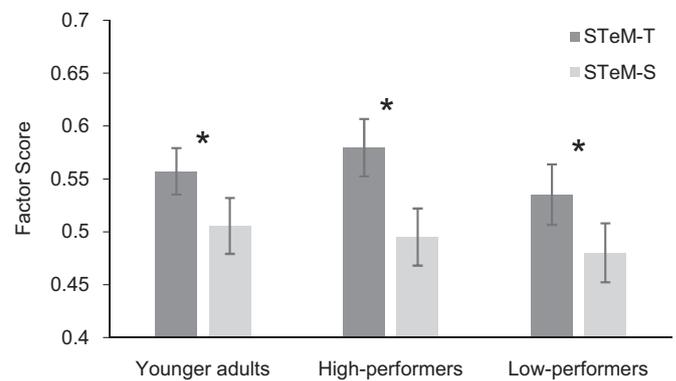


Fig. 3. Temporal (STeM-T) and spatial (STeM-S) factor scores of high-performing and low-performing older adults, and younger individuals on the SteM test. Bars represent standard error and asterisks indicate $p \leq .05$.

A univariate ANOVA was conducted to investigate differences between groups on the SteM total recall. This was non-significant. The two-way mixed ANOVA revealed a statistically significant main effect of clustering (Fig. 3), $F(1, 27) = 6.495$, $MSE = 2.544$, $p = .020$, partial $\eta^2 = 0.194$, and revealed greater preference for temporal clustering compared to spatial clustering, a mean difference of 0.412 (95% CI, 0.080 to 0.743).

3.2. fNIRS data

A three-way mixed ANOVA was performed in order to explore PFC HbO and HHb changes during the retrieval phase of SteM. Contrasts were used to investigate the interactions. There was a significant three-way interaction effect between BA (46, 10, 9), location (right and left hemisphere) and group (younger vs. low-performers vs. high-performers) (HbO: $F(4, 54) = 11.561$, $MSE = 5.540$, $p < .001$, partial $\eta^2 = 0.461$; HHb: $F(4, 54) = 3.215$, $MSE = 1.709$, $p = .019$, partial $\eta^2 = 0.192$). A significant difference in hemisphere oxygenation was found in BA10 (Fig. 4) between right BA10 (HbO: $F(2, 27) = 10.559$, $MSE = 5.515$, $p < .001$, partial $\eta^2 = 0.439$; HHb, $F(2, 27) = 6.700$, $MSE = 3.703$, $p = .004$, partial $\eta^2 = 0.332$) and left BA10 (HbO: $F(2, 27) = 12.854$, $MSE = 6.308$, $p < .001$, partial $\eta^2 = 0.488$; HHb, $F(2, 27) = 2.120$, $p = .140$). Bonferroni corrections were applied for between-subject comparisons and adjusted *p*-values are reported. HbO changes were higher for right BA10 in younger adults (0.788 ± 0.23) compared to the high-performing older group (-0.687 ± 0.23), a mean difference of 1.384 (95% CI, 0.610 to 2.007), $p < .001$, and compared to the low-performing older group (-0.102 ± 0.23), a mean difference of 0.890 (95% CI, 0.065 to 1.714), $p = .031$. HHb changes were greater for right BA10 in high-performing older adults (0.582 ± 0.23) compared to younger participants (-0.629 ± 0.23), a mean difference of 1.211 (95% CI, 0.362 to 2.059), $p = .003$.

Left BA10 showed greater HbO changes in the high-performers (0.282 ± 0.22) and low-performers (0.540 ± 0.22) than in younger participants (-0.946 ± 0.22), a mean difference for high-performers of 1.229 (95% CI, 0.429 to 2.028), $p = .002$, and a mean difference for low-performers of 1.486 (95% CI, 0.687 to 2.286), $p < .001$. The final contrast explored within-group differences when comparing right and left HbO and HHb changes of BA10. This was significant in younger participants, (HbO: $F(1, 27) = 31.037$, $p < .001$, partial $\eta^2 = 0.535$, HHb: $F(1, 27) = 4.506$, $p = .043$, partial $\eta^2 = 0.143$) and in high-performing older adults for HbO ($F(1, 27) = 9.709$, $p = .004$, partial $\eta^2 = 0.264$), but not in the low performing older group. Specifically, younger participants showed greater HbO changes in the right BA10 (0.788 ± 0.23) compared to the left (-0.946 ± 0.22), a mean difference of 1.734 (95% CI, 1.095 to 2.372), $p < .001$. Younger participants also showed greater HHb changes in the left BA10 (0.122 ± 0.27) compared to the right

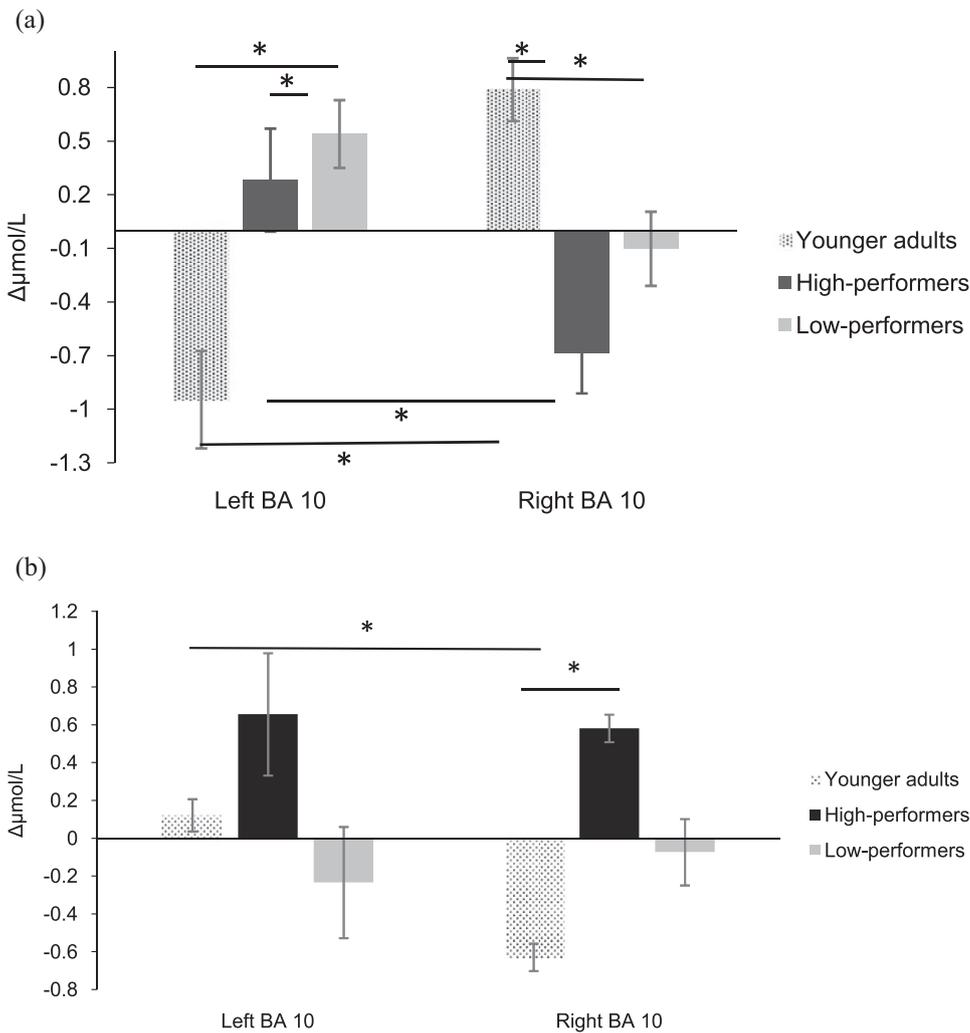


Fig. 4. Mean levels of HbO (a) and HHb (b) in the anterior prefrontal cortex (Brodmann's area 10) amongst groups. Bars indicate standard error and asterisks indicate $p \leq .05$.

(-0.629 ± 0.23), a mean difference of 0.750 (95% CI, 0.025 to 1.475), $p = .043$. High-performing older adults showed greater HbO changes of the left BA10 (0.282 ± 0.22) than the right (-0.687 ± 0.23), a mean difference of 0.970 (95% CI, 0.331 to 1.608), $p = .004$.

4. Discussion

The present study explored the neural substrates of associative processes in memory as consequence of age and the use of temporal versus spatial clustering, within these associative processes. Our results revealed overall preference for temporal over spatial clustering in younger adults and in low-/high-performing older individuals. Although performing alike, each group exhibited differential cortical hemodynamics in the PFC, thus suggesting an effect of age on neurocognitive circuits involved in temporal contiguity. Specifically, older adults recruited opposite (i.e., left) or both hemispheres during memory retrieval of temporal associations, compared to younger adults.

4.1. PFC hemodynamic response

The fNIRS analysis revealed that: 1) younger adults showed an increase of cortical activation in the right anterior PFC, corresponding to BA10, during retrieval; 2) high-performing older participants showed greater cortical activation in left BA10; and 3) low-performing older individuals showed no lateralization. The results of the younger group were in line with previous literature on memory retrieval, such as the HERA model (Tulving et al., 1994), on verbal and non-verbal material

(Habib et al., 2003). Similarly, Okamoto et al. (2011) found greater right PFC blood oxygenation changes during memory retrieval of taste information in younger adults using fNIRS technology. Our results were also consistent with neuroimaging research on memory for temporal context. For instance, Cabeza et al. (1997) investigated age-related differences on PFC activity during temporal context retrieval and found that the right PFC was more active during retrieval of temporal-order information in younger adults, whereas older adults did not show any PFC lateralization.

Previous fNIRS and fMRI studies on older adults suggested aging-related decline in prefrontal activity during cognitive performance (Kwee and Nakada, 2003; Vermeij et al., 2012) and found different PFC activation between age groups (Rajah et al., 2010). This pattern was found in the present study and agrees with the HAROLD model (Cabeza, 2002), where, compared to younger adults, older adults activate bilateral or opposite areas in order to compensate for age-related brain changes. Given that right PFC is usually employed during memory retrieval (Habib et al., 2003), increased activation of left, rather than right, PFC in high-performing older adults suggests that some kind of hemispheric specialization in this group is still present, although through engagement of opposite neural pathways. Low-performing older individuals showed a different pattern, as they employed both hemispheres to achieve memory performance comparable to the other groups, thus suggesting that they may work harder to achieve a performance comparable to their high-performing peers. These results were in agreement with other fNIRS and MRI studies on individuals with neurodegenerative diseases. Fallgatter et al. (1997) and

Grady et al. (2003) reported that older adults with AD showed bilateral PFC activation as an attempt to compensate for losses attributable to neurodegeneration.

Data were baseline-corrected and filters were applied to attenuate noise. Nevertheless, it is still possible that our results were due to false positives and/or negatives (Tachtsidis and Scholkmann, 2016). False positives occur when changes in HbO and HHb are wrongly assigned to a corresponding brain activity, whereas false negatives occur when fNIRS signals are due to extracerebral hemodynamic. In order to address this point, we performed the correlation-based signal improvement (CBSI; Cui et al., 2010) analysis, a method based on negative correlation between HbO and HHb dynamics. The CBSI method has been shown repeatedly to reduce non-evoked systemic influences and to maximize signal quality and the anti-correlation between HbO and HHb (Fairclough et al., 2018; Haeussinger et al., 2014), as in the typical neurovascular coupling (Buxton et al., 1998). The CBSI formula was applied to the raw values of HbO and HHb at each trial, as proposed by Cui et al. (2010), and then averaged over channels and trials, as in the first analysis. The algorithm computed a linear combination of HbO and HHb values, and provided a unique “fNIRS activation signal” (Pinti et al., 2017). The three-way mixed ANOVA was then re-run on the CBSI-corrected signal. The three-way interaction effect was still significant, $F(4, 54) = 7.450$, $MSE = 4.418$, $p < .001$, partial $\eta^2 = 0.356$. Younger adults presented greater activation of the right BA10 (0.989 ± 0.232) compared to the left BA10 (-0.723 ± 0.400), a mean difference of 1.711 (95% CI, 0.776 to 2.646), $p = .001$, and showed again greater activation of the right BA10 compared to both high-performers (-0.654 ± 0.232) and low-performers (0.029 ± 0.232), a mean difference of 1.643 (95% CI, 0.806 to 2.480), $p < .001$ for high-performers, and of 0.960 (95% CI, 0.122 to 1.797), $p = .021$ for low-performers. However, in contrast to our previous analysis, no significant hemispheric lateralization was found in the older groups. These findings confirmed that right BA10 is involved in temporal clustering in younger adults, but also suggest that the lateralization shown by high-performers in the original analysis may have been confounded by undetected noise. The absence of lateralization suggests that older adults may have potentially recruited areas in both hemispheres in order to equal younger adults' performance. This claim is consistent with the CRUNCH model, which suggests that age-related decline causes older adults' brains to recruit more neural circuits in order to achieve performance that is equivalent to that of younger brains, at low levels of task demands. Given that the STeM test requires encoding and free recall of eight items per task, it can be considered a low-demand memory task. However, future research should investigate these claims further, and test whether lateralization does in fact occur in healthy older adults.

4.2. Behavioral performance

The behavioral results showed that younger and high-performing older adults achieved comparable performance on the memory test, including memory total recall and preferential use of temporal clustering. Although unexpected, this was not surprising, as previous research has shown that older adults can perform as well as younger adults, by compensating with alternative neurocognitive networks (Cabeza et al., 2002; Reuter-Lorenz and Lustig, 2005). The low-performing group showed no significant difference on memory performance, either on total recall or temporal contiguity, compared to younger and high-performing older participants. Our hypothesis that low-performers would use spatial clustering as alternative to temporal clustering deficit was therefore rejected, as temporal clustering was consistently preferred throughout memory retrieval.

These comparable results may be caused by several factors. For instance, low-performers were individuals who scored under the average of the average functioning population, but had no diagnoses of neurodegenerative disorders. Therefore, it could be that their memory abilities

were intact at the time of the visit. Alternatively, given that memory performance at delayed recall is considered a stronger predictor than immediate recall of conversion to AD (Gillis et al., 2013; Gomar et al., 2011), it is possible that the fact that the STeM test exclusively used short delays (immediate recall) limited the detection of group differences in associative memory. Finally, although small sample sizes are common in the literature on fNIRS, the absence of group differences in the memory test may be due to a lack of power, as groups of 30 participants were utilized in Gillis et al.'s (2013) cognitive study, where temporal context memory was found to be affected by cognitive decline. Therefore, the findings of this pilot study are to be considered preliminary and should be replicated in bigger samples.

There are other methodological limitations to this study that should be taken into account. Firstly, cortical activation was monitored on the PFC exclusively. Although both the HAROLD and CRUNCH models focus on hemispheric specialization of the PFC, it is well known that other areas of the brain are involved in memory processes (Burke et al., 2014). Future studies may investigate areas of the medial-temporal lobes in order to test whether the compensation hypothesis is applicable to the whole brain. Secondly, as participants' anatomical data were not available, the exact location of the areas investigated may have changed slightly amongst participants. Moreover, our results are limited to two age categories. Since previous neuroimaging studies have shown that brain functionality in response to tasks changes across the lifespan (Reuter et al., 2019), it may be interesting to include other age categories in future studies. Finally, given that other variables are currently being studied as potential predictors of cognitive decline in older adults, such as biomarkers (Lashley et al., 2018) or changes in postural control (Marusic et al., 2019), it may be interesting to explore the dual contribution of these variables and memory organization on cortical activation in older adults. To the best of our knowledge, this was the first study to have used fNIRS to investigate the brain dynamics of temporal clustering during aging. In sum, our observations suggest that prefrontal areas may be involved differentially in temporal clustering in younger and older adulthood. Whilst temporal contiguity seems to be interlinked with the right PFC activity in younger adults, older individuals may recruit alternative networks that permit successful use of temporal associations and therefore efficient memory performance.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Deborah Talamonti: Conceptualization, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Catharine A. Montgomery:** Methodology, Resources, Writing - review & editing, Visualization. **Dan P.A. Clark:** Conceptualization, Methodology, Software, Writing - review & editing. **Davide Bruno:** Conceptualization, Resources, Writing - review & editing, Supervision, Funding acquisition.

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