Neural correlates of episodic memory change in increasing age: a longitudinal event-related potential study

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Lina F. Guerrero[a,b,c], Badiâa Bouazzaoui[a,b,c], Michel Isingrini[a,b,c], Emilie Alibran[a,b,c] and Lucie Angel[a,b,c]

Using a longitudinal design, we examined whether event-related brain potentials (ERPs) correlates of successful episodic memory retrieval varied over a 4-year period according to the level of memory change. ERPs were recorded while participants performed a word-stem cued-recall task, and this procedure was repeated 4 years later. We compared the ERP old/new effect patterns of participants whose memory performance remained stable over time (stable group) with those of participants experiencing episodic memory decline (decline group). The pattern of change of the old/new effect differed between groups. At T1, the two groups exhibited the same pattern, with a positive frontal and parietal old/new effect. For the decline group, the old/new effect pattern did not change between T1 and T2. By contrast, for the stable group, the positive parietal old/new effect at T1 no longer appeared at T2, but a negative old/new effect was exhibited at frontal sites. This brain reorganization pattern could be a compensatory mechanism supporting strategic processes and allowing memory abilities to be maintained over time. *NeuroReport* 32: 268–273 Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

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[a]Department of Psychology, UMR CNRS 7295, Centre de Recherches sur la Cognition et l'Apprentissage, [b]Department of Psychology, University of Tours, 3 rue des Tanneurs, BP 4103 37041 Tours Cedex 1 and [c]Department of Psychology, University of Poitiers, rue Théodore Lefebvre, Poitiers Cedex, France

Correspondence to Lina Guerrero Sastoque, Phd (Pursuing), Department of Psychology, UMR CNRS 7295 Centre de Recherches sur la Cognition et l'Apprentissage, Université de Tours, 3 rue des Tanneurs, 37041 Tours (Functional magnetic resonance imaging), Department of Psychology France
Tel: +33 02 47 36 64 08; e-mail: lina.guerrero@univ-tours.fr

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Introduction

Neural changes associated to episodic memory decline with increasing age have been explored with functional magnetic resonance imaging (fMRI) or event-related brain potential (ERP) methods [1–3]. ERPs of correctly retrieved items classically display a positive deflection compared to correctly rejected new items. This old/new effect, considered as an electrophysiological correlate of retrieval success [3], has three main components: (1) an early fronto-central effect (from about 300–500 ms) associated to familiarity processes; (2) a parietal effect (from around 500–800 ms), classically predominant in the left hemisphere and associated with recollection processes and (3) a late frontal effect (from about 600–1000 ms) reflecting postretrieval monitoring and control processes. Only the parietal and late frontal components seem to be sensitive to the age effect [4–7].

Consistent with the Hemispheric Asymmetry Reduction in OLDer adults (HAROLD model [8]), some ERPs studies observed that the parietal old/new effect becomes distributed more symmetrically across both hemispheres during aging [5,9,10]. In line with the Posterior-anterior shift in aging (PASA model [11]), studies have also identified decreased old/new effect in parietal areas, coupled with maintained or increased effect in frontal areas [4,12]. These patterns appear in middle adulthood and continue to evolve with aging [4]. Additionally, a late frontal negativity (negative deflection for correctly retrieved old items compared to correctly rejected new items) appears with the aging process [6,13,14]. These three brain reorganization patterns may reflect inefficient functioning [6,12,15] or compensatory mechanisms to counteract the negative effects of the aging process [4,5,13].

Almost all these previous studies have used a cross-sectional design. Longitudinal studies would provide greater experimental control and a direct measurement of cognitive and brain changes [16]. The main aim of this study was thus to explore changes in the old/new effect over a period of 4 years, using a longitudinal approach to identify potential neural reorganization patterns and to examine whether these varied as a function of the level of memory change. Participants performed a word-stem cued-recall task while ERPs were recorded. The procedure was repeated 4 years later. In line with previous longitudinal studies showing that episodic memory decline can be observed in as early as the 40 s [17], we included participants aged 40 years and above at baseline. Two groups were constituted based on an index of memory performance change over time (stable vs. decline). We examined (1) the group effect on the old/new effect pattern at baseline (T1) and at follow-up (T2), and (2) whether the old/new effect changed over the 4-year period and whether this pattern of change differed between groups. This approach allowed us to identify potential brain reorganization patterns varying by group and to determine their functional significance.

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Methods

Participants

Twenty-eight adults aged between 42 and 73 years [M (SD): 59.03 years (10.53)] at baseline (T1) were recruited. All were French-speakers, right-handed, and provided their informed consent. They took part in two waves of evaluation: baseline (T1) and follow-up 4 years later (T2). Two groups were constituted according to scores on a Memory Change Index (MCI) (Mdn = –0.135, see behavioral data): a stable group (SG) (scores above the median) and a decline group (DG) (scores below the median). Individuals with an MCI score equal to the median were excluded. Both groups are equivalent in mean age [M (SD): SG: 59.00 (9.65); DG: 59.07 (11.71)] and educational level [SG: 13.71 (4.40); DG: 12.14 (2.93)] at baseline, and in cultural level at T1 and T2 (Mill Hill vocabulary test [18]) [M (SD): SG: T1 = 27.21 (3.59); T2 = 27.63 (2.86); DG: T1 = 27.00 (2.28); T2 = 26.78 (2.62)]. None of the participants had a history of brain injury, cardiovascular disease, psychiatric disease or alcoholism, or were taking medication known to affect the central nervous system. All the participants had scores below the cutoff of 11 on each subscale of the Hospital Anxiety and Depression Scale [19] at T1 and T2. Participants aged 60 years and over scored above the cutoff of 27 on the Mini-Mental State Examination [20]. This study received the approval of the ethics committee of the University of Tours (France).

Material and procedure

A detailed description of stimuli and procedure can be found in Alibran *et al.* [4]. After a short practice session, participants completed four study-test blocks. During each study phase, they were asked to memorize a list of 40 words, presented one at a time, and to complete a concreteness judgment. During the test phase, 60 word stems (first three letters of the words), 40 corresponding to the studied sublists (old) and the remaining 20 to an unstudied sublist (new), were presented. Participants were asked to complete each stem as quickly as possible with a studied word phase, and if that was not possible, with another suitable word. They also had to indicate whether each completed stem was a studied (old) or an unstudied (new) word. The same protocol was used in both waves of evaluation. Continuous electroencephalogram (EEG) activity was recorded from 62 scalp sites using an electrode system fixed in an elastic cap, in accordance with the international 10–20 system [21]. Recorded activity was offline referenced to linked mastoids, and a ground electrode was placed on an anterior site (AFZ). Vertical electrooculogram was recorded from an electrode placed below the right eye and horizontal electrooculogram from two electrodes, one at the outer canthus of each eye.

Data analysis

Behavioral data

A recognition rate index was calculated by subtracting the false alarm rate (proportion of completed stems from unstudied words wrongly recognized as old items) from the recognition rate (proportion of stems from studied words correctly completed and recognized as old). Scores at T2 were adjusted to reduce the practice effect [22]. The same task was performed by an independent sample ($n = 64$) that served as a reference group, matched in age [t (90) = –0.06; ns], educational level [t (91) = 0.18; ns] and cultural level [t (91) = –0.04; ns] with the study sample at T2. Given that cognitive practice effects could vary with age, both the reference group and the longitudinal sample were divided into four age groups (40–49, 50–59, 60–69 and 70–79 years). The practice effect was estimated as the difference between the mean performance of the corresponding age group in the reference sample and the longitudinal group at T2. An adjusted score was then calculated by subtracting the estimated age-related practice effect from the individual memory score at T2.

To estimate episodic memory change over time, we also produced a MCI by subtracting the memory score at T1 from the adjusted memory score at T2, divided by the score at T1. A high index indicated that memory performance remained stable or increased over time.

Event-related brain potentials data

The EEG and electrooculogram signals were sampled continuously at 500 Hz and band-pass filtered between 0.25 and 30 Hz. Offline data were segmented with epochs including a 200 ms prestimulus baseline and a 2000 ms poststimulus interval. Blink artifacts were corrected using Gratton and Coles' algorithm [23], and trials containing muscular or other recording artifacts were rejected manually. ERPs were averaged separately for each group and for old items and new items with a minimum number of 16 artifact-free trials by each condition. Based on previous literature [3,4,13] and on preliminary analyses, mean ERP amplitudes were quantified in four latency windows (300–600 ms, 600–900 ms, 900–1200 ms and 1200–1600 ms poststimulus) and at four electrode sites where the effects were the strongest. For each site, the average of four electrodes was calculated: right frontal (F4, F6, FC4 and FC6), left frontal (F3, F5, FC3 and FC5), right parietal (P4, P6, CP4 and CP6) and left parietal (P3, P5, CP3 and CP5).

Results

Behavioral data

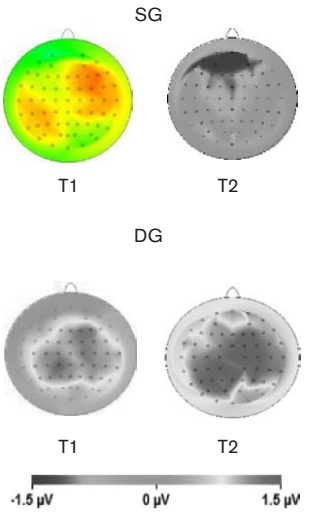
A 2 (group: stable vs. decline) × 2 (time: 1 vs. 2) repeated measures analysis of variance (ANOVA) was performed on the recognition index [m (SD): SG: T1 = 23.39 (11.59); T2 = 25.95 (10.76); DG: T1 = 26.52 (11.26); T2 = 16.69 (10.76)]. It revealed that memory performance declined over time [F (1,26) = 12.78; $P < 0.01$]. The effect of group was NS [F (1,26) = 0.57; ns]. However, the interaction between time and group [F (1,26) = 37.24; $P < 0.001$] revealed that memory performance at T1 did not differ between groups [F (1,26) = 0.52; ns], whereas the SG performed better than the DG at T2 [F (1,26) = 5.23; $P < 0.05$]. Memory declined over time for the DG [F (1,26) = 46.82; $P < 0.001$] but not for the SG [F (1,26) = 3.19; ns]. A t-test

Table 1 Significant results of global ANOVAs comparing old/new effects by each time window and topographic voltage maps showing the magnitude of the old/new effect (old minus new) for the 900–1200 ms time window by time for each group

Old/new effects according to the time and the group F (1,26)				
	300–600 ms	600–900 ms	900–1200 ms	1200–1600 ms
I	–	10.35**	17.72***	20.96***
I×G	–	–	5.72*	7.21*
I×T	–	–	5.95*	–
I×L	–	–	–	6.86*
I×T×G	–	4.24*	12.42**	15.33***
I×G×L	–	5.26*	–	–
I×T×L	–	–	12.38**	–
I×L×H		20.60***	13.17**	–
I×T×G×L	–	–	8.63**	6.97*

Old/new effects between groups (SG vs. DG) for each time F (1,26)				Topographic maps
	600–900 ms	900–1200 ms	1200–1600 ms	900–1200 ms
T1				
I	15.18***	23.57***	19.95***	
I×L×H	7.91*	12.34**	–	
T2				
I	–	-	6.17*	
I×G	–	16.29***	24.23***	
I×L	5.73*	11.62**	9.54**	
I×G×L	5.48*	5.02*	8.68**	
I×L×H	16.51***	–	–	
I×G×L×H	5.41*	–	–	

Old/new effects at T1 and T2 for each group F (1,13)			
	600–900 ms	900–1200 ms	1200–1600 ms
SG			
I	4.85*	–	–
I×T	7.79*	24.27**	17.21**
I×L	–	–	5.39*
I×H	–	–	7.93*
I×L×H	48.53**	15.55***	19.46***
I×T×L	–	12.39*	8.80*
I×T×H	–	–	15.73**
I×T×L×H	–	–	25.16***
DG			
I	5.51*	14.76**	21.20***
I×L	14.14**	–	–



*P<0.05; **P<0.01; ***P<0.001.
I, item type (old vs. new); G, group (stable vs. decline); T, time (T1 vs. T2); L, location (parietal vs. frontal); H, hemisphere (right vs. left).
DG, decline group; SG, stable group.

confirmed an effect of group on the MCI [m (SD): SG: 0.34 (0.78); DG: –.39 (0.26); t (26) = 3.34; P < 0.01].

Event-related brain potentials data[1]

We will describe here only significant main effects or interactions from ANOVAs involving the item type factor (Table 1). No significant effect including the item type was identified between 300 and 600 ms, suggesting that the old/new effect was NS at this time window for any group and at any time window. A significant effect of item type (600–1600 ms) indicated a classical positive old/new effect. The interactions between (1) item type and group (900–1600 ms), (2) item type, time and group (600–1600 ms), (3) item type, group and location (600–900 ms), (4) item type, time and location (900–1200 ms) and (5) item type, time, group and location (900–1600 ms) indicated that the old/new effect, and particularly its anterior-posterior distribution, differed between groups. When necessary, additional between-groups and within-group ANOVAs or post hoc tests using the Newman–Keuls method, with a significance level of P < 0.05. were performed to further explore these interactions.

Between-group comparisons (SG vs. DG) at T1 and T2

T1: A significant effect of item type (600–1600 ms) indicated a classical positive old/new effect. Item type interacted with location and hemisphere (600–1200 ms), indicating that the old/new effect was distributed symmetrically in parietal areas, whereas in frontal areas it was significant only in the right hemisphere (600–900 ms) and was

[1] We computed correlational analyses between the age, and the Memory Change Index (MCI) and the old/new change index over time at each site and time window [old/new effect change=(old/new effect T2 – old/new effect T1)/old/new effect T1; old/new effect corresponded to event-related brain potentials (ERPs) for old items minus ERPs for new items]. Neither the MCI nor old/new change index (all r<0.30; P>0.10) were correlated with age (except for the 600–900 ms window at right parietal site: (r=–.42, P<0.05), suggesting that memory and old/new change were independent of the age variable.

predominant over the right hemisphere (900–1200 ms). No interaction with the group factor was significant, and the old/new effect at T1 was similar in both groups.

T2: A main effect of item type (1200–1600 ms) revealed a classical positive old/new effect. Interaction between item type and location (600–1600 ms) and between item type, location and hemisphere (600–900 ms) indicated an old/new effect distributed symmetrically in parietal areas (600–1600 ms), whereas only significant in the right hemisphere (600–900 ms) in frontal areas. Interactions between item type and group (900–1600 ms), item type, group and location (600–1600 ms), and between item type, group, location and hemisphere (600–900 ms) indicated that the magnitude and the topography of the old/new effect varied between groups. For the SG, a right-sided frontal positive old/new effect, a left-sided frontal negative old/new effect (600–900 ms) and a symmetrical frontal negative old/new effect (900–1200 ms) were observed. In contrast, for the DG, similar to that observed at T1, analyses indicated a symmetrical positive old/new effect in parietal (600–1600 ms) and frontal (900–1600 ms) areas.

Within-group comparisons (T1 vs. T2) in each group (SG and DG)

SG: A significant effect of item type indicated a classical positive old/new effect (600–900 ms). Interactions between item type and location (1200–1600 ms), between item type and hemisphere (1200–1600 ms), and between item type, location and hemisphere (600–1600 ms), revealed a significant right-sided frontal old/new effect (600–900 ms) and a left-sided parietal old/new effect (900–1600 ms). The significant interaction between item type and time (600–1600 ms) indicated that the old/new effect was significant at T1 but not at T2. The interaction between item type, time and location (900–1600 ms) suggests that the positive old/new effect observed in frontal areas at T1 was replaced by a negative old/new effect at T2, and that the positive old/new effect observed in parietal areas at T1 was reduced to a nonsignificant level at T2. The significant interaction between item type, time and hemisphere (1200–1600 ms) indicated a decrease in the magnitude of the old/new effect between T1 and T2, particularly in the right hemisphere. An interaction between item type, time, location and hemisphere (1200–1600 ms) reflected frontal and parietal old/new effects, predominant over the right hemisphere at T1. By contrast, the old/new effect in parietal areas was NS at T2, and a symmetrically distributed negative frontal old/new effect was observed in frontal areas.

DG: A main effect of item type was significant on all time windows, indicating a positive old/new effect in both parietal and frontal areas. The significant interaction between item type and location (600–900 ms) indicated that the old/new effect was greater in parietal than frontal areas. No significant interaction including item type and time was obtained, indicating that the old/new effect did not significantly change over time.

Discussion

The results confirm that episodic memory declines significantly with increasing age, and that this can occur over a period as short as 4 years, consistently with longitudinal studies [17]. However, some individuals maintained their baseline memory functioning (SG), and others exhibited significant memory decline over time (DG), despite the fact that the memory level of the two groups at baseline was the same. At baseline, the two groups exhibited a similar ERP old/new pattern from 600 ms with reliable frontal old/new effects predominant over the right hemisphere and a symmetrical parietal effect consistent with the HAROLD reorganization pattern [8]. However, the old/new effect evolved differentially in the two groups. In the DG, no modification of the ERP pattern was observed, indicating that the same amount of neural activity is associated with reduced memory performance. This suggests that neural activity may have become less efficient over time. By contrast, in the SG, frontal and parietal positive old/new effects observed at T1 disappeared and were replaced by a negative frontal old/new effect at T2, initially left-sided and then symmetrically distributed, suggesting a reorganization mechanism.

These results differ from those of cross-sectional studies, indicating that brain old-new effect-related reorganization patterns, consistent with the HAROLD or PASA models, appear with increasing age [4,5,10]. One possible explanation of this discrepancy is that brain reorganization occurs progressively during the aging process, and different patterns are observed at different ages. Given that the age range of this study was large, we may have identified a brain mechanism common to all the age groups but not the brain reorganization patterns that have been observed for more specific age periods [4]. Even though brain activity could be affected by repeated task exposure, both groups (SG vs. DG) would have been affected similarly by the practice effect, and it is therefore unlikely that this explains between-group differences. Furthermore, the DG did not exhibit any change in the old/new effect pattern over time. Finally, the negative old/new effect at frontal sites in the SG could overlap with the parietal old/new effect, reducing its magnitude, and making it difficult to determine whether there were other concurrent reorganization patterns. It would be interesting to explore whether other brain reorganization patterns would be observed after a longer period between evaluations and with a larger sample size

To our knowledge, the present study is the first to use a longitudinal approach to explore ERP old/new patterns and their change over time as a function of the level of memory change. Patterns of neural modification play a critical role in the change of episodic memory over time; particularly, in this study, frontal negative old/new effect at T2 is associated to less memory decline. This negative old/new effect (beginning about 600 ms poststimulus)

has already been identified in older adults, particularly with source-memory protocols [6,7,13–15], interpreted as reflecting either inefficient neural functioning [6] or a compensatory brain mechanism [13]. Our results suggest a compensatory role, given that it was observed specifically in the group who maintained efficient memory functioning over time. The processes supported by this frontal negativity have not yet been clearly identified but it may reflect the implementation of supplementary control processes, letting to focus attentional resources on the features of stored information relevant for the task, or to use alternative retrieval strategies (e.g. mental imagery) facilitating the recollection of contextual information [7,13,24–25]. However, further studies are needed to confirm this hypothesis by examining the directly strategies that are used during memory tasks.

Given the poor spatial resolution of the ERP technique, limited inferences can be drawn concerning the underlying brain regions of the negative frontal old/new effect. Thus, it would be interesting for further studies to explore the potential generator of this component (e.g. EEG source algorithms, simultaneous EEG and fMRI data). However, it is important to note that some functional neuroimaging studies [26–27] have identified this negative old-new effect in younger adults in different regions, including anterior medial prefrontal, right anterior temporal and right extrastriate cortices. Interestingly, the medial prefrontal cortex would be involved in memory retrieval, decision-making [28] and executive control [29–30], which is consistent with the hypothesis that this negative component could reflect compensatory control processes allowing to improve memory operations. Moreover, in line with the hypothesis that the negative old/new effect underlies control processes allowing us to improve retrieval operations, it could be explored whether it is associated to the frontoparietal network functioning (FNP). FNP, involving dorsomedial prefrontal, lateral prefrontal and superior parietal regions, would support cognitive control processes [31–33]. The identification of the generators of this frontal negative old/new effect would thus allow us to precise the cognitive mechanisms reflected by this component.

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Conflicts of interest

There are no conflicts of interest.

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