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Age-related Task Sensitivity of Frontal EEG Entropy during Encoding predicts Retrieval

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Abstract Age-related declines in memory may be due in part to changes in the complexity of neural activity in the aging brain. Electrophysiological entropy provides an accessible measure of the complexity of ongoing neural activity. In the current study, we calculated the permutation entropy of the electroencephalogram (EEG) during encoding of relevant (to be learned) and irrelevant (to be ignored) stimuli by younger adults, older adults, and older cognitively declined adults. EEG entropy was differentially sensitive to task requirements across groups, with younger and older controls exhibiting greater control of encoding-related activity than older declined participants. Task sensitivity of frontal EEG during encoding predicted later retrieval, in line with previous evidence that cognitive decline is associated with reduced ability to self-initiate encoding-related processes.

Keywords EEG · Memory · Aging · Entropy

1 Introduction

Normal aging is associated with a decline in working memory and episodic memory performance (Hedden and Gabrieli 2004; Salthouse 2011; Schaie 1996). A gradual

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decrease in synaptic density and white matter integrity may contribute to memory deficits (Hedden and Gabrieli 2004; Salthouse 2011) and a number of theories of cognitive aging (Hasher and Zacks 1988; Hogan 2004; West 1996) have identified changes in frontal brain activity as central to an understanding of aging.

One long standing hypothesis that attempts to explain how gradual biological changes give rise to changes in cognitive performance is that an age-related increase in neurological noise results in slower and less accurate performance in older adults (Crossman and Szafran 1956; Welford 1981). Specifically, a lower signal-to-noise ratio within the nervous system results in higher sensory thresholds and slower cognitive performance (Salthouse and Lichty 1985). This lower signal-to-noise ratio may be due to weaker signals propagated by fewer cells or poorly coordinated neural assemblies or greater noise due to poorer inhibition of background activity. Though an age-related increase in neurological noise suggests a parsimonious explanation of poorer cognitive performance, specific tests of this hypothesis have provided equivocal findings (Kail 1997; Salthouse and Lichty 1985; Sosnoff and Newell 2011). Indeed, more recently, researchers (Goldberger 1996; Goldberger, Peng, and Lipsitz 2002; Kaplan, Furman, Pincus, Ryan, Lipsitz, and Goldberger 1991), have proposed that age-related biological changes are expressed in *decreased* neurological and behavioral complexity. The complexity of a system is a consequence of the number of system elements and their functional interactions (Vaillancourt and Newell 2002). A system may decrease in complexity through loss or transformation of system elements or loss or transformation of the functional interactions among elements. In the brain, loss of system elements may occur due to loss of cells or functional assemblies and reduction in functional interactions may occur due to degraded communication between cells or assemblies.

The electroencephalogram (EEG) has been employed in the investigation and diagnosis of cognitive decline for over half a century. In patients with Alzheimer's disease (AD), for example, patients' EEG exhibits a slowing of the dominant posterior rhythm, an increase in diffuse slow activity and reduced alpha and beta power (Brenner, Reynolds, and Ulrich 1988; Gordon and Sim 1967; Jeong 2004; Liddell 1958). The complexity of the EEG signal has been shown to provide valuable diagnostic information. Woyshville and Calabrese (1994) found that single-channel EEG of AD patients exhibited a reduced fractal dimension (D; the original Hausdorff Besicovitch fractal dimension (Mandelbrot 1982)) compared to typical controls, and within the sample of AD patients, autopsy-confirmed AD patients had significantly lower D values than probable AD patients. Later studies (Besthorn, Sattel, Geiger-Kabisch, Zerfass, and Forstl 1995; Jeong, Kim, and Han 1998) employed multiple electrodes and found lower correlation dimension (D2; an alternative measure of fractal dimension) values for AD patients than controls in almost all areas. Jeong et al (1998) also calculated the first Lyapunov exponent (L1), a measure that characterizes the rate of separation of trajectories and that can be considered as a nonlinear measure of predictability, in the EEG signals of AD patients and age-matched healthy subjects and found decreased complexity in the brain activity of AD patients.

The most appropriate method to calculate the complexity of a time series is a somewhat contentious issue (Bhattacharya 2000; Hogan, Kilmartin, Keane, and Collins 2012; Tononi, Edelman, and Sporns 1998) influenced by both practical and theoretical considerations. For instance, some (Abásolo, Hornero, Espino, Alvarez, and Poza 2006) suggest that the amount of data required to compute meaning-

ful values for D2 and L1 makes these indices unsuitable for physiological data. In addition, the algorithms usually employed to estimate D2 assume stationarity, which is relatively rare in biological signals. Alternative approaches to estimating complexity depend to a degree on the concept of entropy as articulated within information theory (Shannon and Weaver 1949). Informational entropy is a measure of the relative probabilities of states of a system such that the more uniform the probability distribution, the greater the entropy. In a purely random series (e.g., white noise), all values are equally probable and therefore entropy is at its maximum, whereas, in a series with only one value, that value has a probability of 1 and entropy is 0. Entropy is related to predictability in that greater entropy typically implies lower predictability. Two major types of estimators have been employed to estimate complexity of EEG signals (Sleigh, Steyn-Ross, Steyn-Ross, Grant, and Ludbrook 2004). The first broad approach to entropy estimation is based on information from the amplitude component of the frequency spectrum (Hjorth 1970; Inouye, Shinosaki, Sakamoto, Toi, Ukai, Iyama, Katsuda, and Hirano 1991; Sleigh et al 2004). The amplitudes of different frequency ranges provide the probabilities for the entropy calculations. The second approach, based on nonlinear dynamics, investigates the properties of the data's phase space, which is usually reconstructed from the EEG time series using time-delay embedding (Izhikevich 2007; Kennel, Brown, and Abarbanel 1992; Packard, Crutchfield, Farmer, and Shaw 1980; Takens 1981; Terman 2005). One kind of entropy relying on phase space properties is the approximate entropy (ApEn; Pincus 1991), which has been shown to be sensitive to changes in EEG due to seizure onset (Srinivasan, Eswaran, and Sriraam 2007) and loss of consciousness (Bruhn, Röpcke, and Hoeft 2000) and to distinguish between the background EEG activity of AD patients and controls (Abásolo, Hornero, and Espino 2005). Sample entropy (SampEn, Richman and Moorman (2000)), a refinement of ApEn, has also been shown to distinguish between the background EEG activity of AD patients and controls (Abásolo et al 2006; Hogan et al 2012) and to distinguish between baseline and task experimental conditions (Hogan et al 2012).

In the current study, we employed permutation entropy as a measure of complexity of the EEG signal. Permutation entropy, a phase space entropy like approximate entropy and sample entropy, was initially introduced by Bandt and Pompe (2002) and it has particular advantages when analyzing event-related EEG. Developed by Bandt and Pompe (2002) as a "[...] natural complexity measure for time series [...]" it has been applied across a broad range of disciplines (Cao, Tung, Gao, Protopopescu, and Hively 2004; Frank, Pompe, Schneider, and Hoyer 2006; Sun, Zou, Nikiforova, Kurths, and Walther 2010). The particular feature of PermEn is that it is based on the local rank relations in the investigated data. For the application of PermEn, the given data is symbolically encoded according to its local rank structure. In physical terms, each symbol corresponds to one partition of the systems' phase space and a change from one symbol to another reflects a transition from one partition to another. The entropy is then computed from the probabilities of the system being in one partition or another, as reflected by different symbols. The prime advantage of this method is that its symbolic encoding routine is rather robust to nonstationarity and slow amplitude transformations, such as drifts in the data. PermEn is therefore resistant to dynamical and observational noise (Bandt and Pompe 2002) and is suitable for shorter time series (Frank et al 2006), such as the EEG within a restricted temporal window correlated with particular cognitive processes. Methods relying on the same symbolization tech-

nique have already been used to analyze EEG data for seizure detection (Groth 2005) and language processing (Schinkel, Marwan, and Kurths 2009). Finally, PermEn is also relatively simple and quick to calculate using freely available software making it a practically useful measure for experimental and clinical neuroscientists (Zanin, Zunino, Rosso, and Papo 2012).

In the context of understanding age-related cognitive decline, measures of permutation entropy may be useful for understanding the dynamics associated with specific problems in either the encoding or retrieval of information or both. For example, research suggests that intentional memorization enhances the encoding of information for later retrieval (Buckner 2004; Craik and Rose 2011). In particular, when participants engage in semantic elaborative encoding of information, the probability that they will remember that information increases (Craik and Rose 2011; Kirchhoff, Anderson, Barch, and Jacoby 2012). A number of findings suggest that older adults find it more difficult to self-initiate effective encoding processes and that this may partly explain poorer retrieval (Buckner, Kelley, and Petersen 1999). Older adults are less likely to spontaneously employ strategies during encoding according to post-experimental reports(Rowe and Schnore 1971), and less likely to use elaborative (semantic) strategies to encode material (Naveh-Benjamin, Brav, and Levy 2007; Verhaeghen and Marcoen 1994). In addition, older adults who are instructed to use semantic strategies while attempting to memorize verbal stimuli use these strategies more frequently than uninstructed older adults and are better able to subsequently recognize verbal stimuli than uninstructed older adults (Naveh-Benjamin et al 2007). Work by Hogan and colleagues (Hogan, Carolan, Roche, Dockree, Kaiser, Bunting, Robertson, and Lawlor 2006) suggests that attempts by AD patients to self-initiate learning can be ineffective, as they found no difference in retrieval of relevant (to be learned) and irrelevant (to be ignored) words presented during encoding. They also found that, although older controls remembered more relevant than irrelevant words, the benefit of a learning cue was significantly greater in the younger control group when compared to older controls.

The self-initiated learning processes described above recruit specific areas in the left frontal cortex (Buckner 2004). Within participants, frontal EEG patterns during encoding distinguish between words that are later remembered and words that are not (Fabiani, Karis, and Donchin 1986; Paller and Wagner 2002). Similar patterns are observed in fMRI studies(Brewer, Zhao, Desmond, Glover, and Gabrieli 1998; Wagner, Koutstaal, and Schacter 1999), in that the level of activity within the frontal cortex predicts whether an item will later be remembered or forgotten. Older adults typically exhibit an under-recruitment of the frontal cortex during encoding (Buckner et al 1999; Logan, Sanders, Snyder, Morris, and Buckner 2002). Impairment of self-initiated learning provides one explanation for this under-recruitment of the frontal cortex during encoding.

In the current study, permutation entropy of the EEG signal during a crucial stage of the encoding process was calculated in order to establish whether there were age-related differences in the complexity of this activity during the processing of relevant and irrelevant words. Three age groups participated in the experiment healthy younger adults, healthy older adults, and healthy older adults with scores 1SD below age- and education-matched peers on standardized tests of memory ability. During an encoding task, participants were presented with both relevant (to be learned stimuli) and irrelevant stimuli in order to highlight possible deficits

in self-initiated learning. By contrasting EEG entropy during presentation of relevant and irrelevant stimuli, it was possible to investigate the task sensitivity of the EEG signals of these three age groups. Entropy was calculated for three regions of interest (ROI), frontal, parietal and temporal, based on previous work (Hogan et al 2012). Hogan and colleagues (Hogan et al 2012) found that sample entropy of the EEG signal was sensitive to task demands, increasing as participants proceeded from pre-experimental Eyes open and Eyes closed conditions to encoding and retrieval conditions. This pattern was observed across samples of varying age and ability (Young, Old and Old declined). However, it has yet to be ascertained whether and how such changes in entropy facilitate cognition. The current study investigated the relationship between participants' EEG entropy during encoding and subsequent retrieval performance to test whether it would provide a potential index of effective self-initiated learning.

2 Materials and Method

2.1 Participants

52 participants (14 young, 19 old, and 19 old who performed 1 SD below age- and education matched peers) completed the study (Mean age=21.9, 73.5 and 72.5 years; Education=15.9, 13.1, 12.9 years, respectively). The 38 older participants were recruited from the National University of Ireland, Galway database of well elderly and the younger participants were psychology undergraduate students at this university. Exclusion criteria included left-handedness, not speaking English as a first language, epilepsy, diabetes, a history of head injury, strokes or TIAs, smoking or taking medication with central nervous system-effects. Those with a history of depression but who were currently not affected were considered for inclusion, as were those who had thyroid problems or hypertension which had been stably controlled for three months or more.

Participants were screened using a number of neuropsychological tests: the mini-mental state exam (MMSE), a memory self-rating scale, the hospital anxiety depression scale (HADS), the national adult reading test (NART), a test of fluency (animal naming), the word reading subtest of the Wide Ranging Achievement Test (WRAT), the Stroop task, and three subscales of the Wechsler Memory Scale (WMS; Logical Memory, Faces and Visual Reproduction). Older adults were placed in the Old group if their WMS memory score was within 1SD of their NART score; older adults whose memory score was 1SD or more below their NART score were placed in the the Old Declined group. The allocation procedure was employed to identify older adults whose memory function was in the early stages of decline relative to age- and education-matched peers.

The young adults scored higher than both old adult groups on the three subscales of the WMS ($p<.001$ for all six comparisons, see Table 1). Older controls scored significantly higher than the older declined group on the logical memory sub-scale ($p<.01$). The younger group had completed significantly more years of formal education than the other two groups ($p<.01$)., but all three groups scored similarly on the NART and WRAT tests of verbal ability. Young adults had higher MMSE scores when compared with old declined group ($p<.05$), but no other differences were observed.

2.2 Procedure

Testing took place over two consecutive days. On the first day, participants completed the neuropsychological screening tests detailed above. On the second day, participants were prepared for EEG recording and completed the encoding and retrieval sessions. Encoding and retrieval employed a computer interface and participants were provided with time and guidance to practice using the interface prior to the encoding session. There was a 30 second delay between the encoding session and the retrieval session. Both encoding and retrieval tasks were coded in E-Prime (Psychology Software Tools, Pittsburgh, PA) which recorded all responses.

2.3 Encoding Task

The encoding task was presented on PC. Following the practice session, participants received instructions that they would see a number of words, some of which they were required to learn and some to ignore. An "L" cue prior to a word meant the word was to be learned, an "X" cue meant that the next word was to ignored. A yellow fixation crosshair was presented in the middle of the screen and participants were requested to look at this when not reading the words. A series of 120 words were presented in white font on a grey background, above the yellow fixation crosshair. Prior to each word, the "L" or "X" cue was presented for 200 ms, followed by a inter-stimulus-interval (ISI) of 1200ms, then the word was presented for 1500 ms. Participants were not required to respond during encoding.

2.4 Retrieval Task

In a test of recognition, 120 words were presented in white font on a grey background above the yellow fixation crosshair, similarly to the encoding task. Of the 120 stimuli, 80 had previously been presented during encoding, 40 were "to be learned" stimuli ("L") and 40 were "to be ignored" stimuli ("X"), and 40 stimuli were novel words not presented during encoding. Participants were instructed to press one button ("Yes") if the word was one that they had previously seen and another it was one they had not ("No"), regardless of whether it had been an "L" or "X" word. Words were presented for 500ms with an ISI of 3500 ms between words and participants responded using an Ergodex response pad.

2.5 EEG recording

The EEG was recorded from 64 active Ag/AgCl ActiCap electrodes (Brain Products GmbH, Munich, Germany) at a sampling rate of 1000 Hz using a BrainAmp AC amplifier (Brain Products GmbH, Munich, Germany) with a gain of 500 and a band pass of 0.5 - 100 Hz. Impedances were kept below 10 $k\Omega$. The electrode placement conformed to the International 10-20 System Committee (1990). A common reference electrode and an anterior scalp ground (Afz) were used. Vertical eye movements were recorded with two electrodes placed above and below the left eye, while electrodes at the outer canthus of each eye recorded horizontal movements.

Trials with artifacts were discarded. Bad channels caused by faulty connections were deleted manually from the continuous EEG recordings. Using Brain Vision, these recordings were then subjected to ocular artifact reduction using blink-averaging algorithms to remove artifactual scalp potentials caused by eyeblinks. Sweeps in which amplitudes exceeded 100 μ V at any scalp electrode were automatically rejected. In total, less than 9% of trials were rejected. All sweeps were baseline corrected using the prestimulus interval as the baseline interval and epoched into single sweep recordings, from -250ms prestimulus to 1000ms post stimulus. The remaining epochs were separated into stimulus category and submitted to entropy analysis. The clustering of electrodes into ROIs is the same as in Hogan et al (2012) Statistical analyses were conducted through R (R Development Core Team 2012) using the following packages: nlme (Pinheiro, Bates, DebRoy, Sarkar, and R Core Team 2012) , ggplot2 (Wickham 2009) and lattice (Sarkar 2008).

2.6 Permutation Entropy Analyses

Permutation entropy was calculated for the period between 100-350 ms post-stimulus. The EEG data for each subject was averaged across trials and permutation entropy was computed from this average signal. To compute the permutation entropy of a given time series the data is symbolised. This is done in the following way: Given an arbitrary timeseries $u(t), t = 1, 2, \ldots, T$ we start by comparing $n = 2$ values – u_t and $u_{t+\tau}$ – separated by a delay of τ. This delay ensures that the points considered are not subject to trivial, linear dependencies. Neglecting tied ranks, $u_t = u_{t+\tau}$, which are rare in real data, the only two rank relations possible are $u_t < u_{t+\tau}$ or $u_t > u_{t+\tau}$. We thus encode the *order pattern* $\pi(t)$ as either 0 or 1.

$$\pi(t) = \begin{cases} 0 \ : \ u(t) < u(t+\tau) \\ 1 \ : \ u(t) > u(t+\tau) \end{cases} \tag{1}$$

For the order $n = 3$, three instances are considered for comparison, namely, $u(t)$, $u(t+\tau)$ and $u(t+2\tau)$. If ties are again neglected, there are six unique patterns possible, which are encoded by integer numbers from zero to five. In general, for an order of n there are $n!$ unique order patterns possible. Applying this procedure to the whole time series $u(t)$ for $t = 1, 2, \ldots, T - (n-1)\tau$ yields a series of order patterns $\pi(t)$ from which we can the compute the probability with which an individual pattern, $p(\pi)$, occurs. The permutation entropy for an order of $n \geq 2$ is then defined as:

$$H(n) = - \sum p(\pi) \log p(\pi). \tag{2}$$

The lower bound of $H(n)$ is 0 which occurs for monotonically increasing or decreasing signals. For random system, in with each permutation/order pattern is equally probable $H(n)$ will reach the upper boundary $\log n!$. Since $H(n)$ is bound by $0 \leq H(n) \leq \log n!$ and hence dependent on the order used. Following the recommendations given in Bandt and Pompe (2002) we therefore use the entropy per symbol, hn, which is defined as:

$$hn = H(n)/(n-1). \tag{3}$$

For the application of the method only 2 parameters are required. The order n determines how many points are used for encoding the rank relations and the delay τ determines the lag between the individual points. For the estimation of these parameters well-established algorithms are readily available. The order is usually estimated using a *false nearest neighbors* approach (Kantz, Schreiber, and Mackay 1997; Kennel et al 1992). In order to better cope with nonstationarities we follow the recommendation by Hegger, Kantz, Matassini, and Schreiber (2000) and used $n = 2\hat{n} + 2$ as the order of the patterns, where $\hat{n}$ is the estimated value. As the delay τ, the first local minimum in the (auto-) mutual information function (Cover and Thomas 1991) is commonly taken. For the current analysis we used an order of $n = 8$ ($\hat{n} = 3$) and a delay of $\tau = 6$.

3 Results

3.1 Entropy

Figure 1 shows the pattern of mean permutation entropy values for each of the three regions of interest (Frontal, Parietal and Temporal) for each age group (Young, Old, Old Declined) and during both tasks (Learn, No Learn). A three-way ANOVA identified a significant three-way interaction between these variables , $F(3.257, 76.544) = 3.2442$, $p = .0233$, eta sq = .03 (Mauchley's Test, $W = 0.7719$, $p = 0.0026$; Greenhouse-Geisser adjusted degrees of freedom) indicating that the differences in entropy between the Learn task and the no Learn task varied significantly across the regions of interest and age group. Significant main effects of ROI, $F(1.5410, 72.423) = 29.60$, $p < .0005$, $\eta^2 = .1555$ ($W = 0.702$, p = 0.0003), and Group, $F(2,47) = 4.608$, $p = .0149$, eta sq = .0610, and an interaction between Group and Task, $F(2,47) = 3.269$, $p = .0469$, eta sq = .0201 were also identified. To situate these values in the context of simultaneous variation in EEG amplitude, grand average event-related potentials (ERPs) are provided for each group and task in Figure 2.

To further investigate these effects, three linear mixed effects (LME) models fit using the maximum likelihood method (using lme from the nlme R package, Pinheiro et al (2012); R Development Core Team (2012)) examined entropy patterns within each ROI. The LMEs specifically tested two hypotheses to explain the Group effect: an age-related hypothesis, using a non-orthogonal contrast between the Young group and the older groups, and a cognitive decline hypothesis, using a non-orthogonal contrast between the Old Declined group and the non-declined groups. In the Frontal ROI, the addition of the Task and Group fixed effects significantly improved the intercept-only model, $\chi^2(9) = 34.98$, $p < .0001$ and a significant Group by Task interaction was found, $F(2,47) = 11.49$, $p = .0001$. Analysis of the contrasts supported the cognitive decline hypothesis; the difference in entropy between the Learn and No Learn task conditions was significantly different in the Old Declined group compared to the non-declined groups, $b = -0.0109$, $t(47) = -3.3472$, $p = .0016$. This can be seen in Figure 1; entropy was lower during the Learn task than the no Learn task for both the Young and Old groups, but, in the Old Declined group, entropy was lower during the No Learn task. The age-based hypothesis was not supported; the Young group were not significantly different from the older groups in the No Learn task condition,

b = 0.0057, t(47) = 1.586, p = .1194. The Group,$F(2,47)$ = 1.33, p = .2737 and Task, $F(1,47)$ = 0.19, p = .6638 main effects were non-significant.

In the Parietal ROI, the addition of the Task and Group fixed effects significantly improved the intercept-only model, $\chi^2(9)$ = 15.83, p = .0074. Even though the overall Group by Task interaction was not significant, $F(2,47)$ = 2.449, p = .0973, analysis of the contrasts again supported the cognitive decline hypothesis; the difference in entropy between the Learn and No Learn task conditions in the Old Declined group was significantly different from the non-declined groups, b = -0.0163, t(47) = -2.166, p = .0354. The age-based hypothesis was not supported; the change in entropy across task conditions in the Young group was not significantly different from that in the older groups, b = 0.0046, t(47) = -0.557, p = .5802. The Group,$F(2,47)$ = 0.427, p = .6552 and Task, $F(1,47)$ = 0, p = .9869 main effects were non-significant. In the Temporal ROI, the addition of the Task and Group fixed effects did not significantly improve the intercept-only model, $\chi^2(9)$ = 2.606, p = .7604, indicating that entropy in this ROI did not vary significantly due to Task or Group.

To summarize, entropy during encoding tasks varied across tasks, groups and regions of interest. Frontal entropy demonstrated greatest sensitivity to task demands and participant characteristics followed by parietal entropy. Old Declined participants exhibited a different pattern of frontal entropy across tasks from the two non-declined groups. The direction of the task-relevant change was different in the frontal and temporal areas in that both Young and Old non-declined groups exhibited a decrease in frontal entropy and an increase in parietal entropy during the Learn task relative to the No Learn task. Temporal entropy did not differ significantly across tasks or groups.

3.2 Retrieval

In order to compare memory performance across groups, a d' score for Learn (d'_L) and No Learn (d'_N)words was calculated based on the following equation.

$$d' = z(pH) - z(pFA) \tag{4}$$

Hits (H) were correct identifications of Learn words (pH_L) or No Learn words (pH_N) and False Alarms (FA) were incorrect responses to novel words. z indicates the z score.

A boxplot of d' values across Group and Task is presented in Figure 3. A linear mixed effects models fit using the maximum likelihood method was used to estimate the effects of Group and Task on the obtained d' values. The addition of these fixed effects significantly improved the intercept-only model, $\chi^2(9)$ = 18.62, p = .0023. There was a significant main effect of Group, $F(2,47)$ = 3.886, p = .0274, but the main effect of Task, $F(1,47)$ = 2.338, p = .1330 and the interaction effect, $F(2,47)$ = 0.1465, p = .8641, were not significant. In this case, analysis of the contrasts supported the age-related hypothesis; the Young group demonstrated significantly better retrieval than the older groups across all task conditions, b = 0.5987, t(47) = 2.218, p = .0315. The Old Declined group were not significantly different from the non-declined groups, b = -0.1301, t(47) = -0.5275, p = .6003.

3.3 Entropy - Retrieval Relationship

The previous analyses demonstrated that permutation entropy in the Frontal ROI was differentially sensitive to task demands across the three groups of participants. Specifically, a drop in entropy during the Learn task compared to the No Learn task was observed in both the Young and the Old group but not in the Old Declined group. We conducted exploratory analyses to investigate whether this drop in entropy (entropy during No learn - entropy during Learn) would provide an index of healthy cognitive function and thus predict retrieval performance. Entropy difference in the Frontal region correlated significantly with retrieval performance in the Learn task for the total sample, $r = .4366$, $t(48) = 3.3619$, $p = .0015$. A moderate but nonsignificant correlation was also observed with retrieval of No Learn words, $r = .2684$, $t(48) = 1.9302$, $p = .0595$. As can be seen from Figure 4, a decrease in Frontal entropy during the Learn task (a positive difference) predicted better retrieval, but this effect was less pronounced in the No Learn task.

Further analyses indicated that the Frontal entropy relationship was stronger in the Young group ($r = .4586$) than in the Old ($r = .2726$), or Old Declined groups, ($r = .2772$). This constitutes preliminary evidence of a moderation effect of age on the relationship between entropy difference and effective encoding. That is, the relationship between task sensitivity of frontal entropy and encoding may differ across age groups. Entropy difference in the remaining two ROIs did not correlate with retrieval of Learn words or No Learn words. As an alternative explanation, we considered whether task sensitivity acted as a mediator of the effects of age and/or cognitive decline on encoding. Due to the small sample size, we employed partial correlations (rather than, for example, structural equation models) to investigate this. The correlation between age (in years) and retrieval was moderately strong, $r = -.4320$, as expected based on the analysis reported earlier, and this reduced when the effect of entropy difference was partialled out, $r = -.3098$. In addition, the partial correlation of entropy difference with retrieval was reduced, $r = .3169$, when age in years was controlled for. This pattern of results suggests entropy difference may partially mediate the effect of age on retrieval. We then dummy coded cognitive decline (Declined and Not Declined) in line with the analyses previously reported. The correlation between cognitive decline and retrieval was weak, $r = .2598$, and was eliminated when entropy difference was partialled out, $r = .0313$. Thus, preliminary evidence of entropy difference as a mediator of the effects of age and cognitive decline on performance was found.

4 Discussion

The current study employed permutation entropy as an index of the complexity of event-related EEG activity during encoding. During the encoding task, younger adults, older adults, and older cognitively declined adults were instructed to learn some words and to ignore others presented sequentially on a computer screen. In line with previous work that has demonstrated that EEG entropy varies across age groups (Hogan et al 2012), ability levels (Abásolo et al 2005; Abásolo et al 2006; Besthorn et al 1995; Hogan et al 2012; Jeong et al 1998; Richman and Moorman 2000; Woyshville and Calabrese 1994) and contexts (Hogan et al 2012), we observed differential task sensitivity of EEG entropy across frontal, parietal and temporal

regions for the three groups in our study Specifically, the Old Declined group exhibited a different pattern of entropy change from the two non-declined groups. In addition, task sensitivity of frontal EEG entropy during encoding predicted whether individuals would later retrieve relevant (i.e., to-be-learned stimuli). These findings supplement the evidence that frontal brain activity (measured through EEG or fMRI) during encoding facilitates retrieval and suggest that task sensitivity of EEG entropy might provide an index of self-initiated learning during encoding.

In the Frontal ROI, EEG entropy decreased for Young and Old control participants when they were presented with Learn stimuli relative to No learn stimuli. The frontal lobes facilitate regulation of information processing demands, and previous work (Hogan et al 2012) has demonstrated large increases in EEG entropy when individuals move from rest to encoding conditions. In the current study, we found that attending to stimuli significantly *reduced* EEG entropy within the encoding situation. However, the difference in direction of entropy change is due to the type of comparisons employed. EEG during resting conditions, especially Eyes Closed conditions, is typically dominated by rhythmic activity (alpha-band), so EEG entropy is relatively low under such conditions. In contrast, in the current experiment, we examined entropy within a relatively short encoding-relevant window. Under such conditions, entropy is higher due to the increased complexity of the demands on the individual. In the encoding situation, a reduction in EEG entropy from this higher level may indicate greater synchronization of neural assemblies required for self-initiated learning.

Within the literature on age-related cognitive decline, researchers have sought to distinguish between cognitive or neural resources that are lost as we age and resources that remain available but are more difficult to access when required (Logan et al 2002). Whereas in the former case (loss of resources), cognitive resources are absent, in the latter case, resources are under-recruited resulting in a production deficiency (Craik and Byrd 1982). In the current study, the task-sensitive reductions in frontal EEG entropy observed in both the Young and Old groups suggest greater neural flexibility and control in these groups. The patterns of EEG entropy in the Old Declined group seem indicative of under-recruitment or compensatory recruitment of resources rather than absence of resources. Specifically, while the Old Declined participants were sensitive to the different conditions during encoding (i.e., entropy consistently varied across conditions), but the patterns of EEG activity were quite different from those observed in the non-declined groups. The Old Declined group were not significantly worse than the Old group in retrieval indicating than for some Old Declined individuals, different patterns of activation may have facilitated retrieval through compensatory processes. Indeed, a limited number of Old Declined individuals with negative entropy differences exhibited much better retrieval than predicted by the overall entropy-retrieval relationship (d' values above the regression line in bottom left panel of Figure 4).

In order to employ a consistent analysis across all ROIs and age groups, we employed simple linear regressions to test for relationships between entropy difference and retrieval performance. A consideration of the scatterplots provided (Figure 4) suggests that for certain ROIs and age groups the relationship between entropy difference and retrieval may not be linear and may not be the same across age groups. It is possible that as the brain ages, such relationships change such that greater or smaller changes in entropy underlie effective encoding. It is also possible that entropy difference is not an equal interval linear determinant of retrieval

performance. For instance, if one considers the scatterplots of the frontal ROI, one might suggest that the relationship between entropy difference and retrieval is exponential with smaller positive entropy differences having a greater effect than larger negative entropy differences. The current analyses highlighted relationships that might be fruitfully explored in greater depth in future research.

The current study highlighted the potential of nonlinear data analysis, in particular permutation entropy, in investigating neural correlates of cognitive performance. However, although we focused on the activity in encoding-associated areas of the brain, the brain is a complex *network* and intricate patterns of activity underlie (and mirror) cognitive processes (Bressler and Kelso 2001; Collins, Hogan, Kilmartin, Keane, Kaiser, and Fischer 2010; Sporns 2002; Tognoli and Kelso 2009). Nonlinear approaches based on phase space reconstruction may enable researchers to highlight patterns of network activity relevant to particular cognitive task. One such method, recurrence quantification, has already been applied to EEG (Schinkel et al 2009; Thomasson, Hoeppner, Webber, and Zbilut 2001) and was recently combined with network analysis (Schinkel, Zamora-López, Dimigen, Sommer, and Kurths 2011). These methods might provide tools to further assess age-related difference in cognitive performance.

Previous researchers have proposed that EEG complexity either increases or decreases with age and reduced cognitive performance. The current study paints a more nuanced picture. In the current study, neither age nor cognitive decline alone reliably predicted complexity of EEG signals during encoding. A main effect of Group was observed when the combination of all three ROIs and both tasks were analyzed, but further analyses at the level of ROI did not support this finding. Rather, groups exhibited differential EEG sensitivity to task requirements, suggesting that younger and older controls had greater control of encoding-related activity than older declined participants, in line with previous evidence that cognitive decline is associated with reduced ability to self-initiate verbal encoding strategies. The pattern of mean entropies observed in the current study replicated the findings of Hogan et al (Hogan et al 2012), who found differences in sample entropy between experimental conditions (e.g., baseline vs encoding) and between ROIs but did not find a straight forward increase or decrease in entropy with age or cognitive decline. In light of their findings, they suggested that in complex systems like a brain, a more adaptive system is one that shows multiple states of relatively higher and lower entropy across different brain regions. The findings of the current study support this position and suggest that it is the task sensitivity of EEG entropy that distinguishes younger adults, older adults, and older cognitively declined adults.

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Table 1: Means and standard deviations (SD) for performance on neuropsychological assessment tasks for young, old, and old decline adults.

	Young (N = 14) Mean *SD*	Old (N = 19) Mean *SD*	Old decline (N = 19) Mean *SD*
Education (years)	15.9 *2.4*	13.1 *3.1*	12.9 *3.0*
NART	17.7 *7.2*	17.9 *10.2*	18.6 *7.4*
Fluency	27.0 *8.4*	17.3 *5.4*	18.6 *4.5*
WRAT	47.8 *3.5*	46.1 *6.5*	45.6 *6.6*

Figure captions

Figure 1

Boxplot (Tukey) of mean entropy for each ROI for each group. The shaded area (box) denotes the interquartile range, the whiskers end at the smallest non-outlier observation ($\pm 1.5 * IQR$) and individual dots represent outliers. Three outlier observations of parietal entropy, one during the Learn task in the Young Group and two during the Ignore (noLearn) task in the Old Declined group were below the minimum entropy limit of this plot.

Figure 2

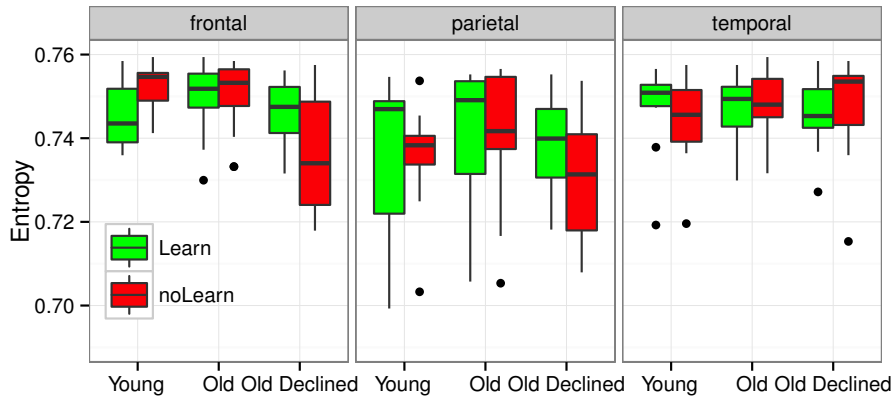
Grand Average ERPs split by ROIs and groups in the learn and no learn condition. For our analyses, we used a time window of 100-350ms after the presentation of the word to be encoded. From the ERPs only a difference in amplitude can be derived. Furthermore the frequency composition of the ERP is similar (see supplementary material). The method we used, permutation entropy, is invariant with respect to amplitude and can reveal more detailed differences in the signals.

Figure 3

Boxplot (Tukey) of retrieval performance across groups and stimulus type. One outlier in the Old group condition scored above the maximum dprime limit on this plot in the Ignore (noLearn) task.

Figure 4

Scatterplots of Entropy Difference (No Learn - Learn) in each ROI against d', a measure of retrieval performance, for Learn words (d'_L) and No Learn words (d'_N). Dashed lines are linear regression lines fit with least squares regression.



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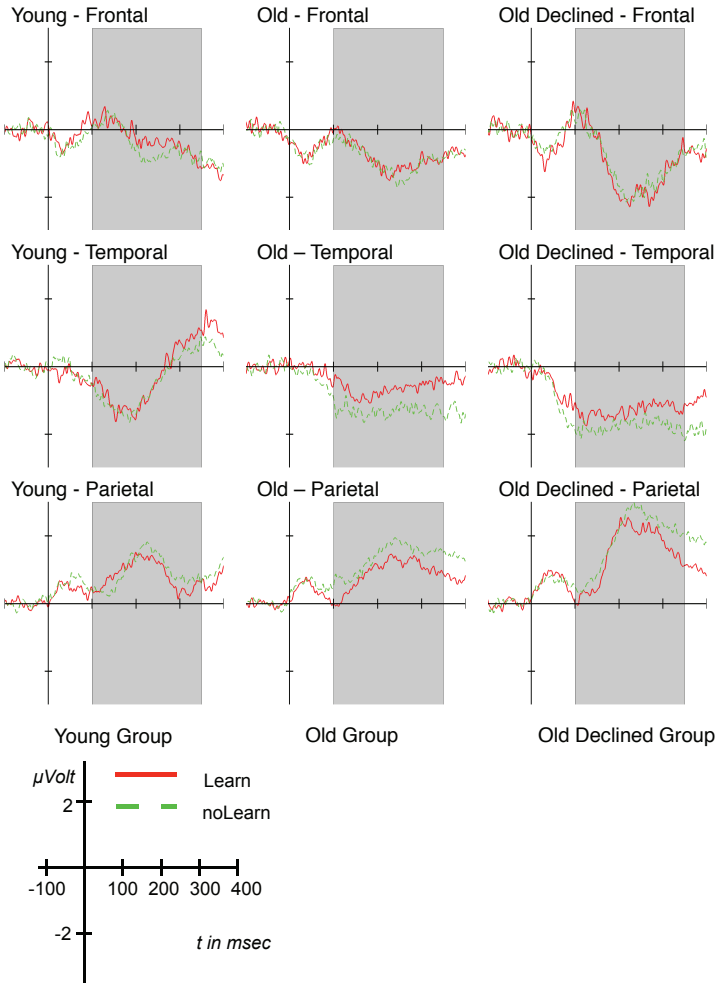

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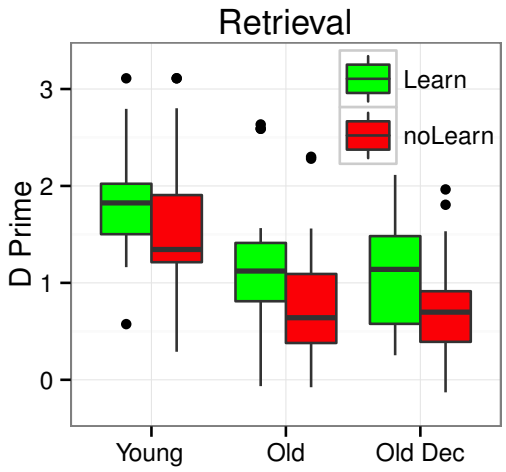

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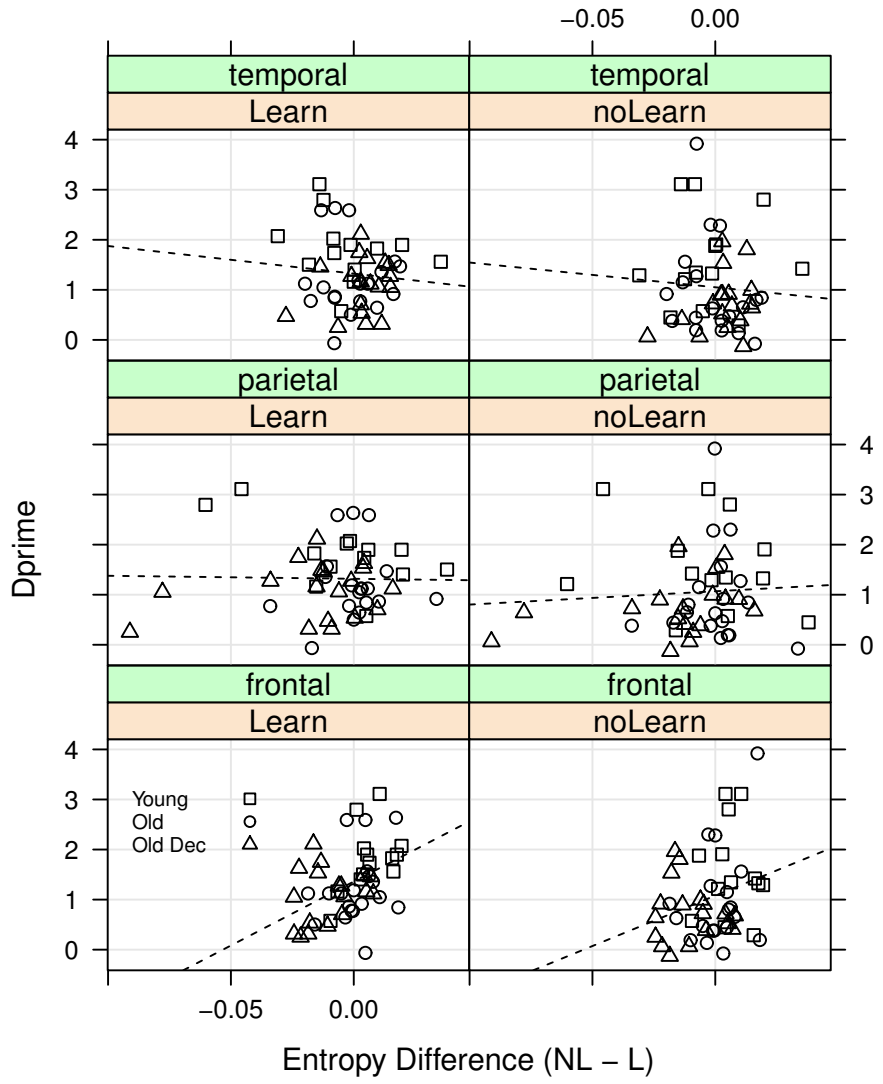

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