

Hogan, M.J., Kilmartin, L., Keane, M., Collins, P., Staff, R., Kaiser, J., Lai, R., & Upton, N. (2012). Electrophysiological entropy in younger adults, older controls and older cognitively declined adults. *Brain Research*, 1445, 1-10.

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Electrophysiological entropy in younger adults, older controls and older cognitively declined adults¹.

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¹ Keywords: Aging, Memory, EEG, Entropy

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Abstract

The current study examined electrophysiological entropy in younger adults, older adults, and older cognitively declined adults across four experimental conditions – eyes closed, eyes open, and during both encoding and recognition of words in a memory task. We hypothesized reduced entropy in older declined adults relative to both older controls and younger adults, with the largest group differences in entropy expected during the encoding and recognition phases of the experiment. We also hypothesised greater hemispheric asymmetry in younger adults compared with older controls and older declined adults. Results revealed significant increases in entropy from eyes closed to eyes open to task. Young adults showed higher entropy in the right relative to the left hemisphere in the temporal lobe and higher entropy in the left relative to the right hemisphere in the parietal lobe. Old cognitively declined adults showed no significant differences between right and left hemisphere entropy. There was a trend whereby older declined adults showed lower entropy than older controls in the frontal lobe, this difference being largest in the left hemisphere during the encoding phase of the experiment. Results indicate that measures of entropy are sensitive to information processing demands and that higher cognitive performance may not be a simple function of entropy level, but rather a combination of level and range, or differentiated range of entropy states across the brain.

There is a great deal of controversy regarding the predictive validity of standard neuropsychological assessments in identifying early cases of dementia (Ritchie & Lovestone, 2002; Ritchie & Touchon, 1992) and the underlying causal factors associated with age- and disease-related decrements in memory and cognition (Anderson & Craik, 2000; Grady & Craik, 2000; Hogan, 2004; Hogan, Swanwick, Kaiser, Rowan, & Lawlor, 2003). Researchers continue to search for a set of biomarkers that will allow for reliable differential diagnosis.

An emerging body of research now suggests that measures of bio-signal complexity and entropy might be useful markers of age- and disease-related cognitive decline. Some researchers have argued that there is a general loss of complexity with aging and disease (Goldberger, Peng, Lipsitz, 2002; Lipsitz, 2002; Kaplan et al., 1991). As a result, the response of these systems is postulated to be less adaptive. At the same time, there is no single mathematical metric which captures the concept of signal complexity, and there are numerous measures of signal entropy (or uncertainty). Indeed, there is significant debate relating to the meaning of the term “complexity” and as to whether many proposed metrics measure complexity or something other than complexity.

Tononi et al (1998) provide an excellent review of the topic of complexity in neural signals and systems and argues that there is an element of subjectivity involved in the selection of criteria used to define complexity for any given system. Nevertheless, Tononi et al (1998) argue that any complexity measure should equally attain very small values when applied to completely random and completely deterministic systems. However, this somewhat strict definition of what constitutes a valid complexity metric is by no means definitive. A significant body of work, including Rezek and Roberts (1998) and Bhattacharya (2000) support a far more

flexible interpretation and propose that quantifying complexity is in fact equivalent to measuring the uncertainty or lack of regularity in a signal.

Utilising this less rigid interpretation of complexity, many different measures, including those based on chaos theory (fractals), symbolic complexity, and entropy metrics have been proposed in a variety of different fields including studies involving the analysis of EEG signals. For example, a chaos based estimate for the uncertainty of an EEG signal, namely the fractal dimension of the waveform (a measure of self similarity at different scales), was reported in Henderson et al (2006) as being suitable for the identification of subjects with Alzheimer's disease (AD). Watanabe et al. (2003) showed that the Liv-Zempel (LZ) complexity (Liv and Zempel, 1978), which is a measure of "symbolic complexity", could be successfully applied to EEG waveforms to distinguish between different gross brain states and different patterns of Event-Related Potentials (ERPs). While there is some convergent evidence across studies which suggest that signal complexity reduces in age- and disease-related cognitive decline, it is unclear if the term "complexity" can be equally applied across all measures used to date. With this in mind, we have restricted our focus here to a description and measure of the signal uncertainty, or conversely predictability, of EEG waveforms.

Notably, one of the most commonly utilised approaches for quantifying the uncertainty of an EEG signal is the calculation of the entropy of the signal. Boltzmann [1844-1906] first described entropy as a measure of the number of microscopic ways that a certain macroscopic state can be realised. Shannon (Shannon and Weaver, 1963) extended this concept to information theory and suggested that information gained in a measurement depends on the number of possible outcomes, of which only one is realised. More unpredictable dynamics have greater entropy; lower entropy systems

are more predictable. Shannon's formulation of the entropy of a signal is in terms of the probabilities of a system being in each of the allowed micro-states and is given in (1).

$$H(S) = \sum_{i=1}^N -p(s_i) \ln p(s_i) \quad (1)$$

Later work by Tsallis (1988) introduced the formulation of a parameterised generalisation of the definition of entropy which is applicable to systems where entropy is non-extensive or non-additive.

In applying formulations of entropy to EEG waveforms, the key issue remains of how to calculate the probability distributions of the states of the system, $p(s_i)$. Many different approaches to this problem have been reported including techniques which implement time-frequency based decompositions of the EEG to form a pseudo-probability distribution function (Rosso et al, 2002) and the estimation of a probability distribution function based on a histogram of time domain EEG samples over the dynamic range of the EEG waveform (Zhao et al, 2007; Loftgren et al, 2007). An alternate time domain estimator of entropy which has been successfully applied to different bio-signals is sample entropy (Richman and Moorman, 2000). This formulation of entropy is based on identifying and quantifying repetitions of similar sequences in the signal waveform and this estimator has been applied to EEG analysis in Abasolo et al (2006).

Entropy indices are potentially useful markers of age- and disease-related cognitive decline. Theoretical models of aging cognition suggest that an increase in the level of intra-network variability may be causally related to the patterns of cognitive decline typically observed in older adults (Li & Lindenberger, 1998; Li, von Oertzen, & Lindenberger, 2006). In their computational models, Li and colleagues have demonstrated that as the signal-to-noise ratio of the system decreases, there is

greater disruption of engaged performance. One potential implication of this reduction in the signal-to-noise ratio is a generalized reduction in adaptive system uncertainty (i.e., the range of possible states the system can achieve in response to adaptive demands) and in the context of perception and memory, less overall capacity to discriminate discrete sensory inputs and retrieve discrete experiences from short- or long-term memory.

A number of studies have already examined EEG entropy in the context of age- and disease-related cognitive changes. Sneddon et al. (2005) measured a specific value of Tsallis entropy using a novel estimator during the recall phase of a delayed memory task and found a reduction in the relative reduction in EEG data predictability in AD but not healthy older controls from posterior (0 – 149 ms) to anterior (150 – 300 ms) recording sites. Sneddon and colleagues concluded that AD results in reduced elaboration of information in frontal brain regions. Zhao et al (2007) reported that the use of a time domain Tsallis entropy estimator applied to long duration background EEG waveforms was successful in producing markers for subjects with Alzheimer's disease. Escudero et al. (2006) reported reduced uncertainty of spontaneous EEG in AD subjects when compared with healthy subjects using a Multiscale entropy (MSE) analysis. However, MSE does not produce a single measure but instead a set of values for each of the time scale values under investigation and, hence, it is necessary to complete a further parameterisation of this set of values (or more typically of the curve formed from these values). Most commonly (e.g. Costa et al., 2005), this parameterisation process involves a piecewise linearisation of the MSE curve in order to produce a variable for subsequent statistical analyses comparing participant groups. Therefore, although MSE appears to provide a useful measure of signal uncertainty and indeed one which appears to meet the strict

criterion of a complexity measure proffered by Tononi et al. (1998), it is a signal representation which is far more difficult to interpret in terms of the underlying physiological processes. In addition, the algorithmic procedure associated with the calculation of MSE is a much more computationally complex process than the calculation of the entropy (using any formulation of entropy) of a windowed section of an EEG signal as utilised by Abasolo et al (2006), Loftgren et al, (2007), Zhao et al (2007) and others. As a result, it is this simpler paradigm of calculating entropy during a windowed section of the EEG which is proposed in this research.

Here, we advance the use of entropy measures for EEG analysis in a number of important ways. First, we measure EEG entropy, as quantified using the sample entropy formulation (Richman and Moorman, 2000), during a post stimulus window during a memory encoding task. This was investigated for subjects in three groups -- healthy younger adults, healthy older adults, and healthy older adults who perform 1SD below age- and education-matched peers on standardized tests of memory ability. If such an event related sample entropy measure is a sensitive marker of age-related cognitive decline, we would expect to see not only differences between younger adults and older adults, but also differences between healthy older adults and older adults whose memory ability is reduced. While previous research has suggested reduced sample entropy in spontaneous EEG in AD subjects when compared with age-matched healthy controls (Abasolo, et al., 2006), it is unclear whether or not event-related sample entropy is sensitive enough to discriminate between older controls and older adults who may be in the very early stages of cognitive decline. In examining differences between our three groups, we were also sensitive to the fact that different brain regions have been implicated in both normal age-related cognitive decline and disease-related cognitive decline, for example, with frontal lobe atrophy being more typical of normal age-related cognitive decline and with temporal lobe

atrophy being an additional critical marker of AD (West, 1996; Hogan et al., 2003). Therefore, to enhance our ability to discriminate between our three groups we measured average sample entropy (that is the sample entropy averaged across a group of regional electrode sites) across the frontal, temporal, and parietal lobes for both hemispheres, separately. In light of previous research on frontal lobe aging (West, 1996; Cabeza, 2002), we explored the possibility that any differences apparent in the resultant sample entropy measures between older controls and older declined adults would be largest in the frontal lobes. We also examined differences in this entropy measure across four experimental conditions – eyes closed, eyes open, encoding, and recognition. If such a regionally averaged sample entropy metric is an index of information complexity, and if EEG complexity reflects information processing complexity, we predicted increases in the sample entropy measure from eyes closed to eyes open, and further increases in the metric during the encoding and recognition phases of our memory task. Furthermore, if the poorer performance of older cognitively declined adults is a function of reduced sample entropy in response to task demands, we would expect to see larger differences between older controls and older declined adults during the memory task than during the eyes closed and eyes open conditions. Finally, as described by the HARLOD (hemispheric asymmetry reduction in older adults) model, when compared with younger adults, older adults show a reduction in asymmetrical activation in response to cognitive challenge (Cabeza, 2002). Therefore, we hypothesised greater hemispheric asymmetry in younger adults compared with older controls and older declined adults. To test these hypothesis, the current study used a 3 (group: young, old, old declined) x 4 (condition: closed, open, encode, retrieve) x 3 (region: frontal, temporal, parietal) x 2 (hemisphere: left, right) ANOVA design to examine group differences in sample

entropy across select brain regions in response to conditions of rest and cognitive challenge.

Methods

Participants

20 young, 17 old, and 18 old who performed 1 SD below age- and education matched peers (Mean age = 21.6, 73.5 and 73.3 years; Education = 16.1, 13.1, 12.5 years, respectively) were recruited with informed consent. Older adults were recruited from the National University of Ireland, Galway, database of well elderly. Younger adults were students studying psychology at the same institute. All participants received a comprehensive medical and neuropsychological assessment (Swanwick et al., 1996; Hogan et al., 2003). Individuals were excluded if they were smokers or if they were taking medication with central nervous system-effects. Also excluded were left-handed people, those who did not speak English as a first language, and those with epilepsy, diabetes, or a history of head injury, strokes or TIAs. 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. Neuropsychological screening tests included: 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). To allocate older adults into the 'normal' and 'impaired' groups, scores on WMS subscales were used. Specifically, scores on these indices were compared to scores on the NART. Scores on the NART provide an estimation of premorbid IQ (Baltes, 1997). Older adults were placed in the 'normal'

group if their WMS memory score was not more than 1SD lower than their NART score; allocation to the ‘impaired’ group was made if the memory score was 1SD or more below the NART score. This system of measurement allowed for the identification of those older adults whose memory function was in the early stages of decline relative to age- and education-matched peers.

The number of years in formal education was significantly longer in the younger group compared with the other two groups ($p < .01$; see table 1 for means and standard deviations). There was no difference between the three groups on either the NART or 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. However, young adults scored higher than both old adult groups on the three sub-scales of the WMS ($p < .001$ for all six comparisons). Older controls scored significantly higher than the older declined group on the logical memory sub-scale ($p < .01$).

Insert Table 1 around here

EEG Task

Eyes closed and open

Participants were asked to remain seated and to relax with their eyes closed for five minutes while their EEG was being recorded. After five minutes they were asked to open their eyes and fixate on a central fixation point ‘X’ on a computer screen. They were asked to remain seated and relax with eyes open while their EEG was being recorded.

Memory Task

During the encoding phase, 120 words were then presented to participants. Each word was presented for 1500ms in white font on a grey background, above a yellow fixation crosshair. An 'L' or 'X' cue, which lasted 200ms, was presented 1200ms before each word. This cue prompted the participant to either learn ('L') or not learn ('X') the word that followed. Six buffer words were presented at the beginning of the task. Participants were instructed to keep their eyes fixed on the yellow crosshair at all times during the task, to prevent disengagement when the 'X' words were presented. Participants were not required to make any responses. During recognition, participants were again presented with words in white font on a grey background above the yellow fixation crosshair. Again 120 words were presented, of which 40 were 'to be learned' ('L') words from the encoding phase, 40 were 'not to be learned' ('X') from the encoding phase, and 40 words were 'new' words not presented previously. Words were presented for 500ms, with an ISI of 3500ms between words. Participants made responses on an Ergodex response pad (www.ergodex.com). Upon the presentation of words in the recognition phase, participants were asked to decide whether the word was presented in the encoding phase, regardless of whether it was an 'L' word or an 'X' word. Again six buffer words were presented at the beginning of this phase. Hits, misses, false alarms, and correct rejections, were recorded automatically by E-prime. Memory performance was assessed by computing hits – false alarms for each stimulus condition (new words, X words, and L words), separately, and expressing results as a percentage.

EEG recordings

Electrophysiological data were recorded in AC mode with a gain of 500 and a band pass of 0.5 – 100 Hz. The sampling frequency used to acquire the EEG signals was

1000Hz (1 kHz). Each participant wore an ActiCAP EEG recording cap connected to the BrainVision EEG recording system. (Brain Products, GmbH, München, Germany) for the duration of the task. Scalp potentials were obtained using a 64-channel array with a common reference electrode and an anterior scalp ground (Afz). The electrode array conformed to the International 10-20 System (American Encephalographic Society, 1994b). 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. Silver/silver-chloride (Ag/AgCl) electrodes were used at all sites. Recording commenced when electrical impedance had been reduced to less than 10kOhms.

Procedure

Medical/neuropsychological and electrophysiological/information processing assessments took place on two separate days. On first arriving in the testing room participants completed the paper and pencil and memory tests. During the second session participants were prepared for the EEG task and provided with an opportunity to practice using the computer interface prior to the task.

Electrophysiological Data Analysis

Bad channels caused by faulty connections were deleted manually from the continuous EEG recordings. These recordings were then subjected to ocular artefact reduction using blink-averaging algorithms to remove artefactual scalp potentials caused by eyeblinks. Sweeps in which amplitudes exceeded $\pm 100 \mu\text{V}$ at any scalp electrode were automatically 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. Incorrect responses and non-responses were manually selected from these EEG sweeps and were excluded from

the subsequent analysis. The remaining epochs were separated into stimulus category and combined to produce grand average waveforms.

Entropy metrics were computed in MATLAB for the eyes closed, eyes open, encoding, and recognition conditions, using the Sample entropy estimator ($m=2$, $r=0.5$). Sample entropy (SampEn) is a measure of the uncertainty of an epoch of an EEG signal consisting of N samples. It does this by estimating the log likelihood that contiguous blocks for m samples from the N samples which are “similar” (i.e. within a tolerance value r using a defined distance measure) remain similar when the block size is extended to $m+1$ contiguous samples. This can be stated as:

$$sampEn(m, r, N) = -\ln\left(\frac{U_{m+1}}{U_m}\right)$$

Where U_m is the conditional probability that the block of N samples is similar for a match length of m samples. For the eyes closed and eyes open conditions the average of 120 randomly selected windows of 250 ms provided the entropy values. For the encoding and recognition phase the 250 ms signal window starting at 100 ms post stimulus was used to calculate the entropy value. Entropy was computed for six regions: frontal left (FP1, AF3, F1) frontal right (FP2, AF4, F2), temporal left (T7, TP7, TP9), temporal right (T8, TP8, TP10), parietal left (P1, P3, PO3), and parietal right (P2, P4, PO4).

Results

Memory

A 3 (group: young, old, old declined) x 3 (stimulus: new word, X word, L word) ANOVA revealed a main effect of group, $F(2, 52) = 3.35$; $p < .05$, with better overall memory (hits – false alarms) in younger adults (46.37%) when compared with both older controls (34.55%) and older declined adults (31.15%; $p < .05$ for both

comparisons). The difference between older controls and older declined was not statistically significant. There was a main effect of stimulus, $F(2,104)=12.07$; $p<.001$, with better memory performance observed for new words (51.21 %) and L words (36.70 %) when compared with X words (24.16 %). The group x stimulus interaction effect was not significant, $F(4, 104) = 1.56$; $p > .05$ (see Figure 1).

Insert Figure 1 around here

Entropy

A 3 (group: young, old, old declined) x 4 (condition: closed, open, encode, retrieve) x 3 (region: frontal, temporal, parietal) x 2 (hemisphere: left, right) ANOVA revealed the a main effect of condition, $F(3, 156) = 22.62$, $p < .0001$, with higher entropy during eyes open (0.35) compared with eyes closed (0.32), $F(1, 52) = 33.13$, $p < .0001$, no difference between eyes open and encoding (0.36), $F(1, 52) = .17$, $p > .05$; and higher entropy during recognition (0.38) when compared with encoding, $F(1, 52) = 8.38$, $p < .005$. There was a main effect of region, $F(2, 104) = 89.18$, $p < .0001$, with lower entropy in parietal lobes (0.31) compared with both frontal (0.37) and temporal lobes (0.38; $p < .001$ for both comparisons). There was a condition x region interaction effect, $F(6,312) = 5.24$; $p<.0001$ (see figure 2). Post-hoc analysis revealed significantly less frontal entropy relative to temporal entropy during eyes closed, $F(1, 52) = 12.11$, $p < .01$, but significantly more frontal entropy relative to temporal entropy during recognition, $F(1, 52) = 10.45$, $p < .01$. Furthermore, while there was a significant increase in entropy from encoding to recognition observed in the frontal lobes, $F(1, 52) = 13.42$, $p < .001$, the concomitant increase in the parietal lobes was less significant, $F(1, 52) = 6.04$, $p < .05$, and there was no observed increase in

entropy from encoding to recognition in the temporal lobes, $F(1, 52) = .09, p > .05$ (see Table 2).

Insert Figure 2 around here

There was a group x region x hemisphere interaction effect, $F(4, 104) = 3.43; p < .01$, with the difference between left and right hemisphere entropy in the temporal and parietal lobes being much larger in younger adults. Specifically, young adults showed a highly significant left-right difference in temporal lobes, $F(1, 52) = 14.81, p < .001$, and parietal lobes, $F(1, 52) = 20.75, p < .0001$, with higher entropy in the right relative to the left in the temporal lobe and higher entropy in the left relative to the right in the parietal lobe. Older controls showed a borderline difference between right and left hemispheres entropy in the temporal lobe in the same direction as younger adults, $F(1, 52) = 3.76, p = .057$. Old declined show no significant right-left differences. The largest mean difference between the older declined adults and older controls was in the right parietal lobes, with older declined having lower entropy (see Figure 3). Post-hoc analysis revealed that this difference was borderline significant during the eyes open and eyes closed, $F(1, 52) = 3.31, p = .07$, and much reduced during encoding and recognition phases, $F(1, 52) = .73, p = .39$. Older declined adults also had lower entropy than older controls in the frontal lobe, this difference being largest in the left hemisphere during the encoding phase of the experiment, $F(1, 52) = 3.61, p = .06$. Younger adults had lower frontal entropy than older controls and lower left temporal entropy when compared with both older controls and older declined adults ($p < .05$ for both comparisons).

Insert Figure 3 around here

Discussion

We examined behavioural and electrophysiological responding of younger adults, older controls, and older cognitively declined adults both during rest and an explicit memory task. Consistent with our expectations, the young adult group performed better than both older controls and older declined adults on the memory task.

Although the two older adult groups differed significantly on the Wechsler Logical Memory Scale, the older controls and older declined groups did not differ significantly on the experimental word memory task.

Consistent with our expectations, we observed an increase in entropy from eyes closed to eyes open to the recognition task, suggesting that entropy indices are sensitive to increases in information processing demands. Furthermore, consistent with the idea that the frontal lobes are critically involved in the regulation of information processing demands (West, 1996; Stuss et al., 2003), the current study revealed that the largest increases in EEG signal uncertainty from rest to task were in the frontal lobes. Also, while there was a significant increase in entropy from encoding to recognition observed in the frontal lobes, this increase in entropy was smaller in the parietal lobes and it was not observed in the temporal lobes.

Unlike previous studies of aging that measured entropy while participants were at rest (e.g., eyes closed) and searched for differences between AD patients and healthy controls across all electrode recording sites, most often reporting significant effects for a smaller sub-set of the full set of electrodes used (cf. Escudero et al., 2006; Abasalo et al., 2006), we examined regions of interest and tested the theoretically-driven hypothesis that older cognitively declined adults would show reduced frontal

lobe entropy during task (encoding and recognition) relative to rest (eyes closed and eyes open). There was a trend for older declined adults to show lower entropy than older controls in the frontal lobe, but this difference only approached significance in the left hemisphere during the encoding phase of the experiment. The largest mean difference between the older declined adults and older controls overall was in the right parietal lobes, with older declined having lower entropy than older controls. Unlike the frontal lobe trend, this difference was largest during eyes open and eyes closed and smaller during encoding.

A number of electrophysiological studies have pointed to changes in both frontal and parietal activations being associated with memory decline in older adults. Wolk et al. (2008) used EEG to examine age-related changes in item recognition memory, finding that early frontal area ERPs were markedly lower for the poorer-performing older group. Gutchess, Ieuiji and Federmeier (2007) compared young and old participants' abilities to recall a scene from memory, finding that recognition levels were unaffected by age, but that the older groups showed lower ERP activations in frontal and parietal areas. Interestingly, this latter finding suggests that, even in the context of similar levels of behavioural performance, patterns of brain activity may help clinicians to distinguish normal older adults from older adults at risk of cognitive decline. Notably, in terms of the comparison between older controls and older declined adults, these findings of Gutchess, Ieuiji and Federmeier (2007) are analogous in certain respects to our findings. In the current study, older controls and older declined adults did not differ significantly on the experimental word memory task, and while this precluded an examination of the relationship between group differences in entropy and group differences in performance, the trend toward reduced

frontal and parietal entropy in older declined adults suggests that there were some subtle brain state differences between the two older adult groups.

Surprisingly, the younger adults in our study had lower left temporal entropy than both older controls and older declined adults and lower entropy in frontal regions when compared with older controls. However, there was also some evidence of greater hemispheric asymmetry in younger adults when compared with older adults. Specifically, while cognitively declined older adults showed no significant differences between right and left hemisphere entropy, young adults showed higher entropy in the right relative to the left hemisphere in the temporal lobe and higher entropy in the left relative to the right hemisphere in the parietal lobe; older controls also showed a borderline difference between right and left hemispheres entropy in the temporal lobe in the same direction as younger adults. This finding suggests a more differentiated (or asymmetrical) pattern of responding in younger adults and older controls relative to older declined adults. This pattern of relatively high right temporal entropy and relatively high left parietal entropy along with lower entropy in the corresponding contra-lateral brain regions may suggest that higher cognitive performance is maintained by a more differentiated range of entropy states across the brain. Notably, the distributed brain activation patterns of younger and older adults can differ in response to similar task demands. For example, as described by the HARLOD (hemispheric asymmetry reduction in older adults) model, when compared with younger adults, older adults show a reduction in asymmetrical activation of the frontal cortex during verbal recall (Cabeza, 2002).

It is possible that the logic of the HAROLD model (which is derived from functional MRI/PET research findings) can be extended to electrophysiological models of aging cognition. Evidence for the HAROLD model is based on stimulus

initiated contrast in functional imaging which is asymmetric in the young and less so (symmetric) in older individuals. The hypothesis suggests that age-related hemispheric asymmetry reductions may have a compensatory function or they may reflect a dedifferentiation process (Cabeza, 2002). It may well be that the changes we observe are compensatory or dedifferentiation in origin. The findings in the temporal and parietal lobes are consistent with compensation/dedifferentiation that involves the contra-lateral hemisphere. The findings in the frontal lobe are less straight forward. The literature has shown a significant functional imaging contrast asymmetry in the frontal lobe (Cabeza, 2002). This is not reflected in the entropy measures and highlights the point that differences in entropy are not synonymous with differences in contrast. Nevertheless, if one assumes that more distributed patterns of brain activation are associated with more random signal output, then the higher levels of entropy in older adults when compared with younger adults are consistent with a more complex underlying mechanism brought about by compensation and dedifferentiation.

Although the results of the current study are not consistent with the broad claim that there is a general loss of complexity with aging, it is important to note that Goldberger et al. (2002) in making the claim that complexity reduces with aging and disease focused largely on comparisons of disease and non-disease states in older adults rather than comparisons of healthy younger and older adults. Notably, some of the studies that have compared healthy younger and older adults have used cardiovascular data and not EEG data (e.g., Kaplan et al., 1991). Furthermore, as noted in the introduction, while research and theory suggests that measures of electrophysiological signal complexity and entropy might be useful markers of age- and disease-related cognitive decline, the majority of the studies have compared Alzheimer's Disease patients with healthy age-matched controls (Sneddon et al.,

2005; Escudero et al., 2006; Abasolo, et al., 2006). Thus, while previous research has suggested reduced sample entropy in spontaneous EEG in AD subjects when compared with healthy age-matched controls (Abasolo, et al., 2006), we were less certain if event-related sample entropy would be sensitive enough to discriminate between older controls and older adults who may be in the very early stages of cognitive decline, or if the cognitive performance differences we anticipated when comparing younger and older adults would map easily onto differences in EEG entropy.

Drawing upon the existing research literature and the computational models of Li and colleagues (Li & Lindenberger, 1998; Li, von Oertzen, & Lindenberger, 2006) we hypothesized not only a reduction in adaptive system uncertainty, or entropy, in older declined adults relative to older controls, but also a more generalized reduction in entropy with age, that is, in the comparison between younger and older adult groups, particularly in the frontal lobes. Interestingly, we observed differences between older controls and older declined adults in the hypothesised direction, but a mixture of lower entropy and a more differentiated pattern of entropy level across regions in the younger adults when compared with older adults. In the context of EEG signal properties, it may not be a simple case of older adults showing less entropy than younger adults, it may be more complex than this. It may be 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. Future research might use principle component analysis of a multi-dimensional set of regional entropy values and compare younger and older adults to examine if younger adults show greater dimensional complexity in this regard. However, it is likely that larger sample sizes than used in the current study would be needed for comparison

purposes. We are currently exploring the application of network analysis to EEG data and the comparison of younger and older adults in particular. It is possible that not only the factorial structuring of entropy is more complex in younger adults when compared with older adults, but also that the network linking one region to another is different. One possible way of examining this issue would be through the use of Joint\Cross Recurrence Analysis.

Modelling aging memory involves modelling its neurological and information processing resource base. Some theoretical models suggest that generic properties of brain function, for example, the level of intra-network variability, may be causally related to the patterns of age- and disease-related cognitive decline (Li & Lindenberger, 1998; Li, von Oertzen, & Lindenberger, 2006). The idea that entropy may be of general functional significance comes from studies that have found reduced uncertainty associated with a variety of age-related chronic conditions (Goldberger, Peng, Lipsitz, 2002; Lipsitz, 2002; Kaplan et al., 1991). Entropy measures may help to characterize vulnerability in aging in a way that conventional approaches which require a stimulus or task and the measurement of some contrast be it using fMRI, EEG or MEG, are unable to assess. Entropy has been suggested as an indication of system vulnerability in a number of other fields such as Electromyography (Akkurt et al., 2009) and Electrocardiography (Pincus, 1995), where differences in entropy are observed independent of any stimulus. Further research with older adults should focus on extracting a range of more specific indicators of entropy across multiple sites and multiple experimental conditions, such that the functional significance of entropy can be assessed more fully. As noted in the introduction, there are multiple interpretations of the true meaning of the term “complexity” and many offer a quite restrictive interpretation of this term. Even when restricting the terminology to the more general

concept of signal uncertainty, many different measures have been proposed to quantify this metric and much work needs to be done to better understand how best to extract, combine, and use these different measures. Further research in this area should seek to develop novel electrophysiological strategies that record time- and performance-related changes in brain activity. In this way, we can work to develop a better understanding of the brain dynamics undergirding individual differences in both average performance and performance fluctuations. While entropy measures may prove useful to clinicians who seek to identify and characterize patterns of age-related cognitive decline, considerable work needs to be done to further our understanding of the relationship between age-related decline, compensatory brain activity, and the limits of compensatory brain activity in the face of decline.

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Table 1. Demographics and neuropsychological assessment score means and standard deviations (SD) for the three groups.

	Younger adults		Older adults		Older adults declined	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	21.68	3.06	73.55	4.07	73.3	4.7
Education (years)	16.14	2.4	13.15	3.08	12.5	3.05
National adult reading test	18.27	6.71	17.45	10.12	18.6	7.19
WRAT	47.41	3.58	46.45	6.53	45.75	6.42
Wechsler Logical Memory II	28.18	1.37	25.65	2.46	21.65	5.65
Total Recall	89.5	15.2	51.2	17.98	42.05	24.08
Copy Total Score	103.27	0.88	98.45	4.95	97.1	5.96
MMSE total	29.36	1.09	28.35	2.25	28	1.81

Note: MMSE = Mini Mental State Examination; WRAT = Wide Ranging Achievement Test.

Table 2. Mean (Standard deviation) entropy values for the young, old and old decline groups for the four conditions -- eyes closed, eyes open, encoding, and recognition -- and for the right and left hemispheres of the three regions: frontal, temporal, and parietal.

		Young			Old			Old Decline		
		Frontal	Temporal	Parietal	Frontal	Temporal	Parietal	Frontal	Temporal	Parietal
Closed	Left	.31 (.063)	.34 (.089)	.29 (.118)	.35 (.083)	.36 (.087)	.30 (.087)	.33 (.089)	.35 (.072)	.28 (.081)
	Right	.31 (.093)	.38 (.090)	.25 (.083)	.35 (.095)	.37 (.083)	.30 (.098)	.33 (.091)	.37 (.078)	.25 (.092)
Open	Left	.35 (.049)	.35 (.064)	.35 (.095)	.37 (.062)	.38 (.079)	.33 (.071)	.37 (.066)	.39 (.074)	.30 (.088)
	Right	.36 (.069)	.41 (.105)	.29 (.066)	.40 (.078)	.40 (.044)	.35 (.097)	.37 (.078)	.38 (.076)	.30 (.110)
Encode	Left	.35 (.046)	.35 (.064)	.34 (.077)	.41 (.070)	.39 (.060)	.35 (.075)	.36 (.081)	.40 (.056)	.31 (.083)
	Right	.36 (.075)	.36 (.063)	.29 (.071)	.41 (.063)	.41 (.055)	.33 (.074)	.38 (.061)	.39 (.068)	.30 (.079)
Recognition	Left	.40 (.053)	.36 (.068)	.37 (.085)	.42 (.068)	.39 (.063)	.36 (.088)	.42 (.086)	.39 (.076)	.35 (.082)
	Right	.38 (.063)	.38 (.060)	.32 (.087)	.41 (.068)	.41 (.059)	.34 (.080)	.40 (.068)	.40 (.063)	.33 (.066)

Figures

Figure 1. Recognition memory of younger and older adults to Learn and No Learn Words.

Figure 2. Entropy across four experimental phases in the frontal, temporal, and parietal lobes averaged across all participants.

Figure 3. Entropy in younger, older controls, and older declined adults in right and left hemispheres in frontal, temporal, and parietal regions.



