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RESEARCH ARTICLE

Investigation of changes in EEG complexity during memory retrieval: the effect of midazolam

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Abstract The aim of this study is applying nonlinear methods to assess changes in brain dynamics in a placebo-controlled study of midazolam-induced amnesia. Subjects injected with saline and midazolam during study, performed old/new recognition memory tests with EEG recording. Based on previous studies, as midazolam causes anterograde amnesia, we expected that midazolam would affect the EEG's degree of complexity. Recurrence quantification analysis, and approximate entropy were used in this assessment. These methods compare with other nonlinear techniques such as computation of the correlation dimension, are suitable for non-stationary EEG signals. Our findings suggest that EEG's complexity decreases during memory retrieval. Although this trend is observed in nonlinear curves related to the midazolam condition, the overall complexity were greater than in the saline condition. This result implies that impaired memory function caused by midazolam is associated with greater EEG's complexity compared to normal memory retrieval in saline injection.

Keywords Nonlinear analysis · Recurrence quantification analysis (RQA) · Approximate entropy · Memory · ERP

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Introduction

One way to study memory is comparing the performance of normal subjects to subjects with impairments (e.g. Cohen and Squire 1980; Scoville and Milner 1957; Weiskrantz 1970). Differences in performance can be used to infer that a given impairment might affect a specific brain mechanism or cognitive process that is thought to underlie memory. A number of conditions lead to memory impairment (broadly defined), but the focus of this research is to investigate changes in brain dynamics in impairments of episodic recognition memory due to the temporary influence of the drug Midazolam.

Midazolam is a short-acting bezodiazepine central nervous system (CNS) depressant. Benzodiazepines are drugs with anxiolytic, sedative, and muscle relaxant properties (Buffett-Jerrott and Stewart 2002; Curran 1986). These drugs also produce 'anterograde amnesia'—forgetting of information learned after drug administration. In contrast, benzodiazepines do not induce 'retrograde amnesia'—forgetting of information learned before drug administration (e.g. Twersky et al. 1993).

Midazolam is known to impair the explicit memory abilities of adult patients undergoing conscious sedation while leaving their implicit memory abilities intact (e.g. Polster et al. 1993). It appears that midazolam induces dissociation between explicit and implicit memory (Stewart et al. 2006). Furthermore some studies found that midazolam disrupts the mirror-patterned word-frequency effect for recognition memory by reversing the typical hit-rate advantage for low-frequency words (Hirshman et al. 2002). Using a computational model, Malmberg et al. (2004) suggest that midazolam decreases the accuracy with which memory traces are stored.

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Memory theories based on such observations might, however, be constrained by the auxiliary assumptions concerning how a given impairment affects brain and cognitive processes. That is, deeper insights might be available by combining such empirical explorations with EEG analysis.

Event Related Potentials (ERPs) are specific patterns of electrical changes extracted from EEG, which are known to correspond with cognitive processes. They can inform our understanding of information processing in the brain (Donchin et al. 1978). For example, many studies on recognition memory used ERP signals have shown that ERPs reliably differ between correctly classified old (items that have already been studied, Called "Hits") and new items (that have not previously been studied and usually called as "Correct Rejections") starting $\sim$300 ms after stimulus onset (Friedman et al. 2000; Rugg and Allan 2000). Several studies have reported two different ERP components: a mid-frontal ERP old/new difference peaking at $\sim$400 ms ("FN400 old/new effect") and a parietal old/new difference peaking at $\sim$600 ms ("parietal old/new effect"). The FN400 ERP effects analyzed within superior, anterior regions of interest (Fig. 1, LAS and RAS) from 300 to 500 ms, has significant difference whit more positive amplitudes for old than new items. Furthermore, the parietal ERP effects within superior, posterior regions of interest (Fig. 1, LPS and RPS) from 500 to 800 ms shows greater amplitudes for old items than new one. These effects were observed for old/new items in midazolam. Especially, in parietal effects, there was a significant difference between saline and midazolam conditions. The average ERPs for all subjects/trials has been shown in Fig. 2.

Since EEG results from a spatial integration of activity of large formations of neurons (Nunez 1981), and they are known to be nonlinear devices because of their sigmoid activation function (Kandel et al. 1995), it seems EEG should be treated as nonlinear time series. Applying nonlinear techniques of data analysis to EEG measurements has a long tradition. Most of these efforts have been done by computing the correlation dimension of spontaneous EEG (e.g. Babloyantz et al. 1985; Rapp et al. 1986; Gallez and Babloyantz 1991; Lutzenberger et al. 1992; Pitchard and Duke 1992). While correlation

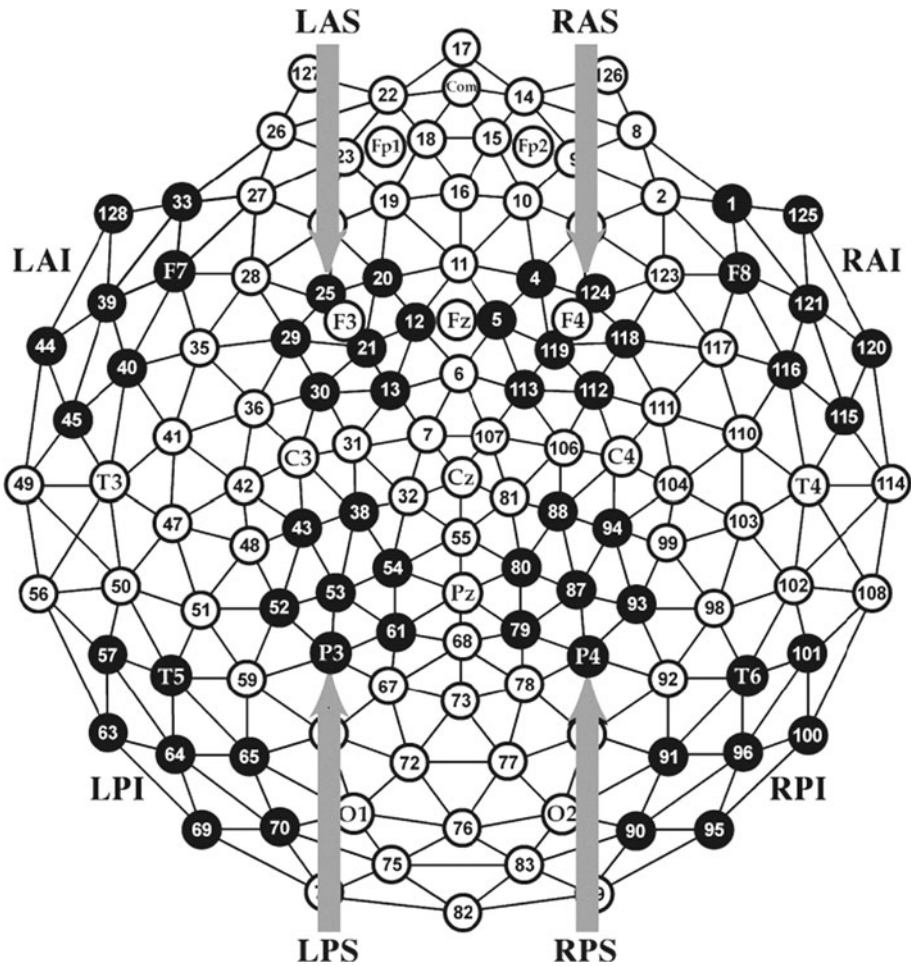

Fig. 1 Location of regions of interest used in analysis are shown by *arrows*

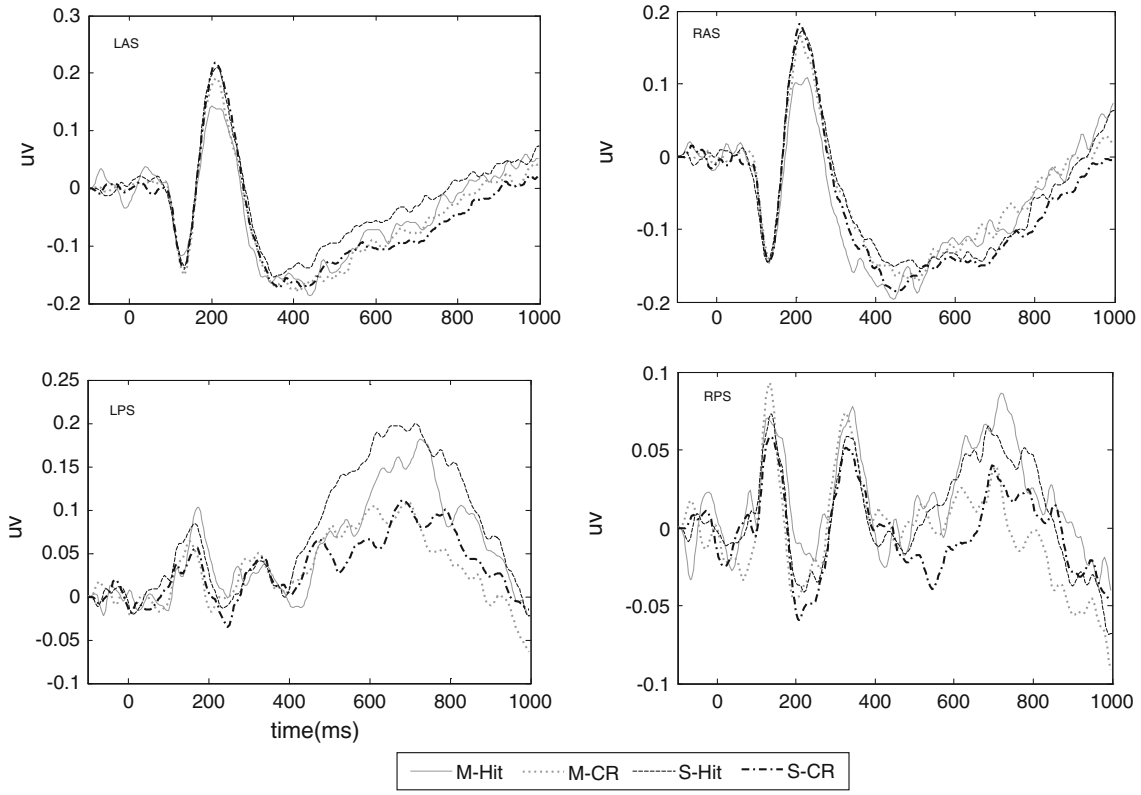

Fig. 2 ERP waveforms. Grand-averaged ERPs are shown for each condition (saline/midazolam-old/new), averaged within the regions of interest used in the analyses. Region locations are shown in Fig. 1 (LAS, RAS, LPS, RPS)

dimensions are only well defined for stationary time series generated by a low dimensional dynamical system moving around an attractor, these measures fail in investigating EEG (Sutton et al. 1965), because they are non-stationary by definition [time-dependent changes of EEGs power in different frequency bands, which is modeled by allowing the variances of the driving noises to change with time (Wong et al. 2005)].

Applying the concepts of the recurrence quantification analysis (RQA) to EEG data could be one way of dealing with this problem. RQA is a non-linear analysis method based on recurrence plots (RPs). The main advantage of this method is that it can be used for non-stationary signals. RQA has been used in previous EEG studies. For example Thomasson used RPs on EEGs to predict seizure (Thomasson et al. 2001). Marwan et al. applied extended RQA to data from single-trials of the oddball experiment, and detected transients in EEG signals around 300 ms, corresponding to p300 component (Marwan and Meinke 2002; Marwan et al. 2007). The N400 is also detected using Order Pattern Recurrence Plots by Schinkel (2007). Instead of using the spatial closeness between phase space trajectories, order patterns recurrence plots use order patterns π for the definition of a recurrence.

The approximate entropy (ApEn) is also useful for short, noisy time series because it is capable of providing a robust, model-independent, information-theoretic estimation of dynamical complexity (Pincus 1991, 1995). Prior studies have shown that EEG-based ApEn can be a sensitive discriminator of various neurophysiological states or conditions such as sleep, anaesthesia, epilepsy, depression and Alzheimer's disease (Radhakrishnan and Gangadhar 1998; Hornero et al. 1999; Bruhn et al. 2000; Levy et al. 2003; Abasolo et al. 2005; Burioka et al. 2005a, b). In the study of Chen et al. 2008, there was a significant difference between ApEn computed for deep coma and brain death conditions. According to previous studies, the ApEn measures the complexity of the EEG and may indicate the degree of arousal (Stam 2005).

In a previous study we used RQA to assess brain dynamic changes during an intact memory retrieval process (Talebi and Nasrabadi 2010). We used EEG signals from subjects who were injected with Saline. We found a decrease in brain complexity during memory retrieval. Our measurements expressly showed a complexity reduction onset 400 ms after delivering of the recognition memory test stimuli.

In this paper, we used RQA and ApEN to investigate changes in brain complexity during impaired memory

performance, and compare it with the result of our previous study for intact memory. Data was from a placebo-controlled study: Subjects were injected by saline and/or midazolam immediately prior to studying a list of words. After the drug had worn off, approximately 70 min later, subjects were asked to label the test words as old or new. Based on previous studies we hypothesize that midazolam would affect the EEG. This study addresses the question of whether the complexity of brain dynamics would also change during impaired memory performance. Are there differences between old and new nonlinear features in midazolam condition, and if so, do they differ from saline? Finally, are brain dynamics affected by midazolam more or less complex than the saline condition?

The first section off this study consists of a short introduction into RQA and ApEn. In the next section this method will be used for single-trial EEG recorded during memory recognition test in saline/midazolam administration. The nonlinear measures will be computed for these signals and finally these measures compared in four different Old/New and saline/midazolam conditions.

Method

Data

The data used in this article was previous published along with a standard ERP analysis (Curran et al. 2006). Twenty students of University of Colorado participated in the experiment. Each subject participated in two sessions (once with saline and once with midazolam, double-blind). Stimuli were 480 low-frequency English words. The words were divided randomly into four 120-word sets that appeared equally often in each condition (old/new-by-midazolam/saline). Each word was displayed in the center of a computer monitor for 4 s, with a 1 s inter-word interval. During the recognition memory task, scalp voltages were collected with a 128 channel high-input impedance amplifier. Amplified analog voltages (0.1–100 Hz band-pass) were digitized at 250 Hz. Recording starts 100 ms before stimulus onset and continued 1,000 ms after that. The EEG was digitally low-pass filtered at 40 Hz. Trials were discarded from analyses if they contained incorrect responses, eye movements (electrooculogram over 70 μV), or >20 % of channels were bad (average amplitude over 100 μV or transit amplitude over 50 μV). EEG was measured with respect to a vertex reference (Cz), but an average-reference transformation was used to minimize the effects of reference-site activity and accurately estimate the scalp topography of the measured electrical fields (Picton et al. 1995; Dien 1998).

Data analysis

Recurrence quantification analysis

The method of recurrence plots (RP) was introduced to visualize the time dependent behavior of the dynamics of systems, which can be pictured as a trajectory in the phase space (Eckmann et al. 1987). It represents the recurrence of the *m*-dimensional phase space trajectory xi $\in R^m$ (i = 1,…, N, time discrete) to a certain state. The main step of this visualization is the calculation of the N × N-matrix

$$R_{i,j} := \left(\varepsilon - \left\|\overrightarrow{x_i} - \overrightarrow{x_j}\right\|\right); \quad i,\ j = 1,\ldots,N; \tag{1}$$

Where, $\overrightarrow{x_i}$ is a trajectory of system in its *m* dimensional phase space, ε is a cut-off distance, ‖.‖ is the norm of vectors, Θ is the Heaviside function and N is the number of states. Usually the phase space has to be reconstructed from the original one-dimensional time series (Takens et al. 1981, Packard et al. 1980). Because analysis of system's trajectory in phase space is dependent on the embedding dimension, *m*, it has to be chosen appropriately.

In a recurrence plot there are three small scale structures: single points which can occur if states are rare; a diagonal line of length *l*, $\left(\mathbf{R}_{i+k,j+k} \equiv 1 \middle| \begin{matrix} l-1 \\ k=0 \end{matrix}\right)$, occurs when a segment of the trajectory runs almost in parallel to another segment (i.e. through an ε-tube around the other segment), and a vertical (horizontal) line with *v* the length of the vertical line $(\mathbf{R}_{i,j+k} \equiv 1 \middle| \begin{matrix} v-1 \\ k=0 \end{matrix})$, marks a time interval in which a state does not change or changes very slowly. In order to go beyond the visual impression yielded by RPs, several measures of complexity which quantify the small-scale structures in RPs have been proposed in some studies (e.g. Webber et al. 1994; Marwan et al. 2002) and are known as *recurrence quantification analysis* (*RQA*). A computation of these measures in small windows (submatrices) of the RP moving along the LOI[1] yields the time dependent behavior of these variables. *Recurrence rate* (*RR*), based on the recurrence point density, is simply the average number of neighbors that each point on the trajectory has in its ε-neighborhood. The measures based on diagonal line distribution are *determinism (DET), Average diagonal line length* (L_{mean} *or* <*L*>), the *longest diagonal line* ($L_{\max}$) and *entropy (ENTR).* The diagonal line distribution encodes main properties of the system, such as predictability and measures of complexity. The more a system is determined the greater amplitude of these measures. Finally measures based on vertical lines structures are *laminarity* (LAM), *trapping time* (TT), and *maximal*

[1] Line Of Identity $\left(R_{i,i} \equiv 1\big|_{i=1}^{N}\right)$.

length of the vertical lines (v_{max}). Measures based on vertical lines, marks state where trapped for some time. This is a typical behavior of laminar states.

As was mentioned before, for RQA, the reconstructed signal in phase space is required. Embedding dimension, m, is an important parameter and has to be chosen correctly. *Correlation dimension* and *false nearest neighbors* are two common approaches to estimate the smallest sufficient embedding dimension. Both of these methods return the same $m = 4$ for saline and midazolam EEGs (EEGs recorded during saline and midazolam sessions). We used spatial embedding to reconstruct the state space of the system. In this case the m coordinates of the state space vectors are taken as the values of the m time series at a particular time; by repeating this for consecutive time points a series of vectors is obtained. The connection between successive vectors defines the trajectory of the system. In this case the embedding dimension m (4 in this study) is equal to the number of channels used to reconstruct the vectors. We took central electrode from each region [LAS, RAS, LPS and RPS (Fig. 1)] respectively. These four regions were originally used in Curran et al.'s (2006) ERP analysis. Measures of complexity were computed using moving window along the LOI, yielding the time dependent behavior of these variables. Computing these measures depends on several parameters. The most important of them is threshold, ε. A common method is to choose ε as 10 % of the maximum phase space diameter, which in this article is used. In addition parameters l_{min},v_{min}, size of moving window w, and Thiler window size should be selected properly (Thiler and spurious 1986, Marwan and Meinke 2002). In this study we considered $v_{min} = l_{min} = 4$, moving window size $w = 200$ ms, and Theiler window size 2. RQA computation was performed for both saline and midazolam EEGs with the same parameters (e.g. embedding dimension, ε, l_{min},v_{min}, etc.).

Approximate entropy

ApEn is an index that quantifies the irregularity or complexity of a dynamical system. It is particularly effective with short and noisy time-series data. ApEn measures the logarithm of the frequency with which neighborhoods of temporal patterns of length m within a certain distance r in phase space remain close together ($<r$) for patterns that are augmented by one time point (i.e. for patterns of length $m + 1$). Thus, smaller values of ApEn imply stronger regularity or persistence in a time series. Conversely, larger values of ApEn signify greater fluctuation or irregularity in a time series.

ApEn is computed from the correlation integral $C_i^m(r)$, which represents the number of points within a distance r from the ith point of the time series when the signal is embedded in an m-dimensional space, that is, when embedded in a phase space with embedding dimension m:

$$C_i^m(r) = (N - (m-1))^{-1} \sum_{j=1}^{N-(m-1)} \Theta(r - |X_i - X_j|) \qquad (2)$$

Where $\Theta(t)$ is the Heaviside function (if $t \geq 0$, $\Theta(t) = 1$; if $t < 0$, $\Theta(t) = 0$) and X_i and X_j are vectors in phase space, embedded from the time series.

These two vectors represent size-m vectors (or temporal patterns) of x values at regular intervals, beginning with the ith and jth points, respectively. ApEn is defined as

$$ApEn(m, r) = \Phi^m(r) - \Phi^{m+1}(r) \qquad (3)$$

Where

$$\Phi^m(r) = [N - (m-1)]^{-1} \sum_{j=1}^{N-(m-1)} \ln C_i^m(r) \qquad (4)$$

In this study we computed ApEn for 200 ms-windowed embedded signal, and shifted the window through the time. Here, we selected $m = 4$ and $r = 20$ % of the standard deviation (SD) of the EEGs as suitable values; these values are based on a previous study showing their validity for estimating ApEn (Abasolo et al. 2005; Sohn et al. 2010).

Result

Applying RQA on data showed an increase in the measurements, indicating decreases in signal's complexity, after presentation the test stimuli. This reduction was greater for correctly recognized old (hits) than new items (correct rejections), and these changes in brain complexity were observed either in saline EEGs or in midazolam signals. Figure 3 shows the average RR % of all trials of all subjects. The onset of the increasing of the parameters is about 200 ms before the event. This is due to the windowed analysis of the RPs (200 ms windows). We have chosen the beginning of the RP window for the time, which results in a 200 ms earlier onset of the RQA variables. Actually, 400 ms after stimulation RQA variables start to increase, reflecting a reduction in system's dimension and complexity (Fig. 3: each point of this curve is the result of computation during 200 ms later than it (Talebi and Nasrabadi 2010). These changes in complexity are consistent with occurrence of ERP component (i.e. FN400). As it is obvious in Fig. 3, the increase in the amplitude of *Recurrence Rate* (*RR*) is also observed after delivering a stimulus in the midazolam condition, but it is less than changes in saline-related *RRs* (the amplitude increment of *RR* was 17 % in saline/old, 9 % in saline/new, 14 % in midazolam/old, and 7 % in midazolam/new). In addition, the

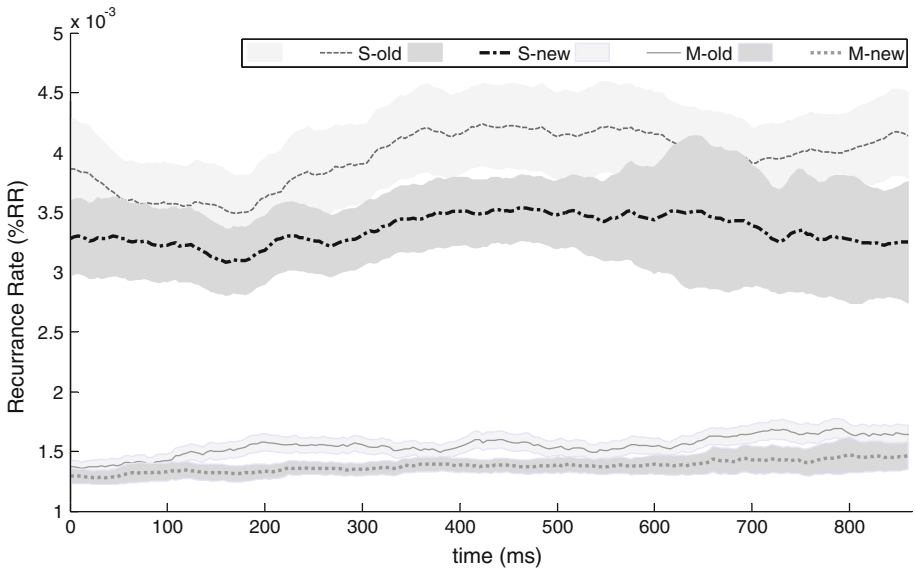

Fig. 3 Recurrence rate for Saline/Midazolam-Old/New signals, averaged for all trials. Because of windowing, the onset of the increasing of the parameters is about 200 ms before the event. The light gray band marks the 95 % confidence interval. (*S-old* saline-old, *S-new* saline-new, *M-old* midazolam-old, *M-new* midazolam-new)

difference between old and new items is more distinct in saline (77 % of p values were less than 0.05) than midazolam (49 % of p values were less than 0.05). Furthermore, the overall magnitude of *RR* is greater for saline related curves than midazolam's. All of these results imply that impaired memory retrieval performance (caused by midazolam) corresponds with higher complexity compared to controls (saline condition).

As it mentioned before, RQA measures computed in moving windows, allow us to study the change of them with time, which can reveal transitions in the system. Whereas the diagonal-wise defined measures (DET, ENTR, <L>, and L_max) are able to find chaos-order transitions (Trulla et al. 1996), the vertical-wise defined measures (LAM, TT, V_max) indicate chaos–chaos transitions (Marwan et al. 2002). The more a system is determined the greater amplitude of these measures. As you see in Fig. 4, both groups of measures consistently reveal that in the ERP data, there are transitions from less determined (or laminar) states to more regular states after the occurrence of the event. Furthermore, the difference of all RQA measures between saline and midazolam condition is significant, indicate the difference in brain complexity between intact and impaired memory performance, respectively.

ApEn was estimated for the same reconstructed signals in phase space used in RQA. The results have been averaged on all trials of all subjects. Figure 5 shows the mean values of ApEn with their 95 % confidence interval for the saline/midazolam—old/new conditions. It can be seen that in midazolam injection, subjects had greater ApEn than in saline. In this case, the amplitude decrement of *ApEn* (7 % in saline/old, 10 % in saline/new, 12 % in midazolam/old, and 11 % in midazolam/new), and distinction between old/new groups (midazolam: 63 % of p values less than 0.05, vs. saline: 58 % of p values were less 0.05) was more in midazolam than saline. However, there is significant overlap of confidence intervals shown in Fig. 5, which cause less distinction than the case of RQA. The results also suggest that EEG activity is more regular (less complex) in times that memory retrieval happened. Like the RR curves, because we used a windowed signal of length 200 ms, the ApEn decreases before 400 ms.

Discussion

The notion of 'complexity' as a nonlinear EEG analysis has been applied extensively to study the cortical dynamics of various conditions. The amount of EEG's complexity carries important information about the structured components of the data, such as oscillatory components. Such structured components may be helpful for understanding of EEG dynamics (e.g. prediction/detection of epileptic seizures from EEG, Gao et al. 2011, diagnosis of Alzheimer's disease (AD), Dauwels et al. 2010, performance of visual cortex, Hu et al. 2011, Working memory dynamics, Colliaux et al. 2009, etc.).

For more clarification of 'complexity' one can refer to two new concepts introduced by Stam (2005). The first is the functional source, which is defined as the part or parts of the brain that contribute to the activity recorded at a single sensor. A functional source is an operational concept, which does not have to coincide with a well defined anatomical part of the brain, and is neutral with respect to the problems of source localization and volume conduction; it is simply shorthand for denoting the part of the brain being measured at a single recording site. The second concept, a functional network, is then defined as the full

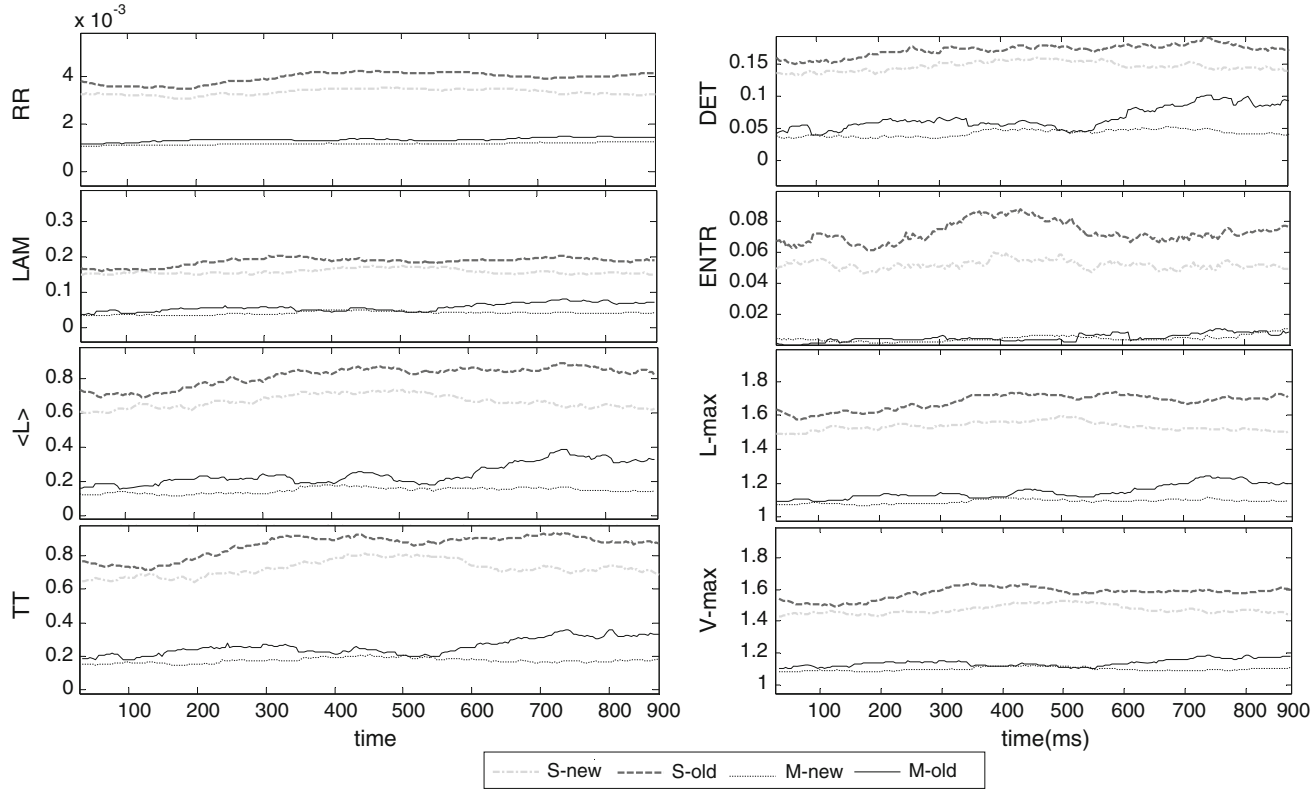

Fig. 4 RQA measures computed for Saline/Midazolam-Old/New signals. Analysis performed for single trial EEGs but in this figure we showed averages on all trials. As it clear amplitudes of all measures are greater in saline signals, implying less complexity than midazolam

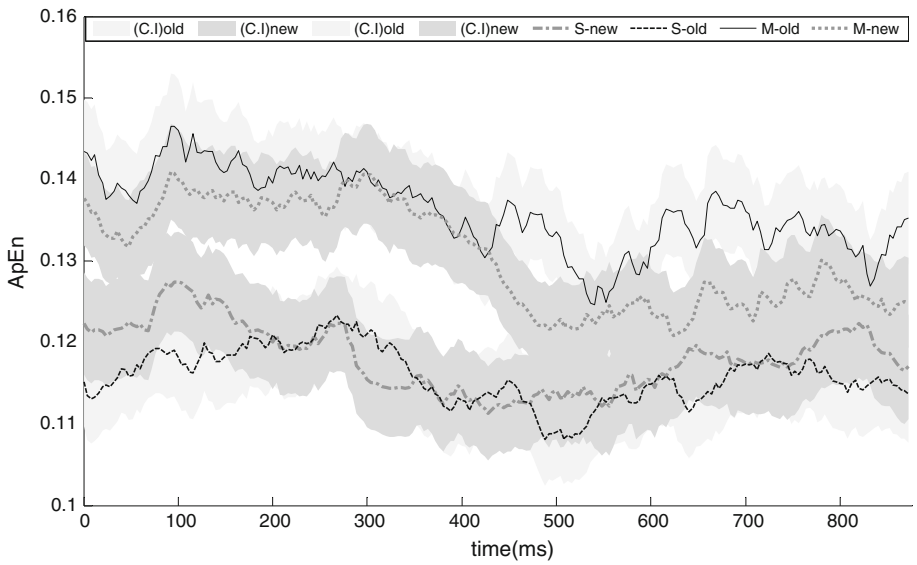

Fig. 5 Approximate entropy: mean and 95 % confidence interval (CI) values for Mdz/Saline-old/new conditions (*S-old* saline-old, *S-new* saline-new, *M-old* midazolam-old, *M-new* midazolam-new). ApEn decreases during memory retrieval. Because we use 200 ms-window signal, complexity decrement is shown before 400 ms. Note that ApEn for midazolam old/new is greater than saline, implying more EEG's complexity

matrix of all pair-wise correlations between functional sources. So 'dynamical complexity' can be defined as the randomness or lack of interactions between the elements of a dynamical system. This definition can be easily translated to the functional source/functional network terminology introduced above: 'dynamical complexity' of a functional network is related to the lack of correlations between its functional sources. Alternatively we can state: the higher the level of synchronization between functional sources in a functional network, the lower its dynamical complexity.

The EEG results from the summation of postsynaptic activity of a large number of spatially distributed but

functionally connected and interacting cortical neurons and neuronal assemblies i.e. functional sources (Anokhin et al. 2006). Accordingly, the EEG time series has a complex structure reflecting the complexity of the underlying neural generators (Lutzenberger et al. 1992; Pritchard et al. 1995). A greater number of independent processes contributing to the EEG results in a greater complexity of EEG time series (Lutzenberger et al. 1995). EEG complexity may reflect the number of states of a system resulting from the interaction among its elements, with higher complexity reflecting a larger number of separable oscillatory networks (Tononi et al. 1998). On the other hand, the complexity of the system's dynamics can be thought of as a measure of the degrees of freedom.

In this study we have analyzed the EEG activity by means of RQA and ApEn. Subjects participated in two sessions of memory retrieval test (once with midazolam injection which causes memory impairment and ones with saline that leaves memory intact). The RQA and ApEn advantage compare with some nonlinear methods like computation of correlation dimension is that they do not need any stationary assumption about signals and are suitable for non-stationary short length EEG signals. These nonlinear measures, as indexes of complexity, showed that during memory retrieval, EEG's complexity decreases. This reduction is indicated by decrease in ApEn values, and increase in RQA measures. Note that as a signal become more regular, recurrences of trajectories in phase space occurred more, and resulted RQA measures have higher amplitude. In other hand, loss of irregularity or complexity causes reduction in ApEn value. This result implies that either recognizing an studied old item, or trying to identify an unstudied new item, which both involve memory processes in brain, cause a decrease in EEG complexity. Although RQA measures suggest that recognizing studied words decreases complexity more than non-studied words, this was not confirmed by ApEn. Nevertheless, both methods reveal that EEG's complexity is greater in impaired memory function compared to normal processing.

Midazolam is a benzodiazepine, which causes a decrease in accuracy of memory storage. (Benzodiazepines inhibit the firing GABAergic interneurons in the hippocampus (Deadwyler et al. 1979). Hence, if Midazolam inhibits the firing of those cells that regulate the orderly firing of the vast majority of hippocampal cells, then it is reasonable to speculate that the result is a noisier episodic memory trace. Because of this noisier episodic memory trace, it is acceptable that the complexity of the signal is higher following midazolam than saline, reflecting impaired memory retrieval and a higher degree of randomness in brain dynamics underlying recognizing an item.

Nevertheless, several studies report an increase in the correlation dimension or related complexity measures during cognitive tasks (Bizas et al. 1999; Meyer-Lindenberg 1998; Micheloyannis et al. 1998, 2002; Molle et al. 1995; Stam et al. 1996; Tomberg 1999). However, decreases in complexity have been reported, most notably during a working memory task (Molnar et al. 1995; Sammer 1996, 1999). Sammer showed that a working-memory load induced by a memory-scanning task has an effect on nonlinear descriptors of the EEG dynamics. The effect was locally specific above the fronto-temporal (right) cortex and it was described as a reduction in the dimensional complexity of cortical brain activity. In an investigation of Kirsch and his co-workers, it was showed that the complexity of the signal under cognitive challenge is higher in schizophrenic patients than in normal control subjects, reflecting the impaired information processing abilities of the patients. For that EEG complexity measure no differences occurred under the baseline condition. In contrast, during the first minute under task conditions the control subjects showed a decrease of the dimension while no changes were found for the schizophrenic group (Kirsch et al. 2000).

Although both methods show this trend, but RQA has better distinction between old/new groups than ApEn (Fig. 3, 5). Furthermore difference of impaired and normal memory in RQA measures is more significant than ApEn values (RQA: average saline/Mdz difference = 47 %; ApEn: average saline/Mdz difference = 6 %). It seems that RQA properly follows dynamical changes in brain functions, and can be a powerful tool to reveal hidden characteristics of EEG signals.

Further work is now required to test the potential value of RQA and ApEn prospectively, i.e. apply them to a new and larger data set or comparison of these methods in the EEG of cognitive processes with other nonlinear quantifiers.

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