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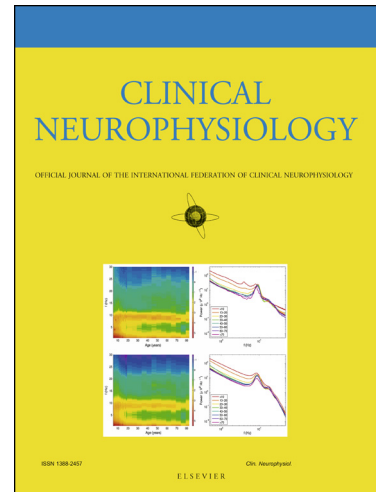
Discovering EEG resting state alterations of Semantic Dementia

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PII: S1388-2457(16)00067-5  
DOI: <http://dx.doi.org/10.1016/j.clinph.2016.01.025>  
Reference: CLINPH 2007749

To appear in: *Clinical Neurophysiology*

Accepted Date: 3 January 2016



Please cite this article as: Grieder, M., Koenig, T., Kinoshita, T., Utsunomiya, K., Wahlund, L-O., Dierks, T., Nishida, K., Discovering EEG resting state alterations of Semantic Dementia, *Clinical Neurophysiology* (2016), doi: <http://dx.doi.org/10.1016/j.clinph.2016.01.025>

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## Discovering EEG resting state alterations of Semantic Dementia

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### Highlights

- First evidence of altered EEG resting state in Semantic Dementia.
- Topographical comparison of resting state EEG microstates between Semantic Dementia, Alzheimer's Disease, and healthy elderly.
- Altered microstate class found in Semantic Dementia is related with decreased MMSE scores.

### Abstract

*Objective:* Diagnosis of semantic dementia relies on cost-intensive MRI or PET, although resting EEG markers of other dementias have been reported. Yet the view still holds that resting EEG in patients with semantic dementia is normal. However, studies using increasingly sophisticated EEG analysis methods have demonstrated that slightest alterations of functional brain states can be detected.

*Methods:* We analyzed the common four resting EEG microstates (A, B, C, and D) of 8 patients with semantic dementia in comparison with 8 healthy controls and 8 patients with Alzheimer's disease.

*Results:* Topographical differences between the groups were found in microstate classes B and C, while microstate classes A and D were comparable. The data showed that the semantic dementia group had a peculiar microstate E, but the commonly found microstate C was lacking. Furthermore, the presence of microstate E was significantly correlated with lower MMSE and language scores.

*Conclusion:* Alterations in resting EEG can be found in semantic dementia. Topographical shifts in microstate C might be related to semantic memory deficits.

*Significance:* This is the first study that discovered resting state EEG abnormality in semantic dementia. The notion that resting EEG in this dementia subtype is normal has to be revised.

**Keywords:** EEG; EEG microstates; semantic dementia; Alzheimer's disease; resting state.

## 1. Introduction

Semantic dementia (SD) is a variant of the Frontotemporal Lobar Degeneration (FTLD), a spectrum of non-Alzheimer's dementias (Neary et al., 1998). It is characterized by a progressive language disorder with fluent, empty spontaneous speech, and loss of word meaning, commonly manifested by impaired naming and semantic paraphrases. Following this, SD has also been referred to as the semantic variant of primary progressive aphasia (Gorno-Tempini et al., 2011). According to the diagnostic guidelines of this clinical syndrome, it also encompasses a variety of symptoms such as loss of sympathy and empathy, and narrowed preoccupations (Snowden et al., 2001, Rankin et al., 2005).

Brain imaging methods, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) show brain tissue atrophy and hypoperfusion in orbitofrontal and temporal lobes (Galton et al., 2001, Chan et al., 2002, Rosen et al., 2002, Diehl et al., 2004). Approximately 60% of the patients with SD show left lateralized atrophy and one third asymmetrical atrophy to the right hemisphere (Brambati et al., 2009). These regionally limited pathological changes circumscribe the unique character of this clinical syndrome. In particular, patients with left side atrophy show the typical semantic dysfunction, whereas right atrophied patients show dysfunctions of object recognition, or even the inability to recognize their family members' faces (Gorno-Tempini et al., 2004).

Although MRI and PET provide invaluable insight in the neuropathology of SD, they are costly and invasive in the case of PET. In contrast, electroencephalography (EEG) is a non-invasive technique highly sensitive to changes in the functional state of the human brain. Due to its high temporal resolution, EEG is advantageous in the detection of rapidly and subtle changing brain activations as compared with other methods such as functional MRI (fMRI). Commonly, EEG recordings can be divided into two approaches. One approach is used to assess spontaneous brain activity where subjects are at awake rest, also referred as resting-state. The other approach involves stimuli or tasks to evoke brain activity patterns, so-called event-related potentials (ERP). Contrasting varying task or stimulus conditions allows the investigation of

specific perceptive or cognitive functions. Despite these advantages, resting EEG has neither been used to investigate the electrophysiological mechanisms of SD nor validated for a clinical purpose. Instead, the guidelines declare only that resting-state EEG is normal in SD (Neary et al., 1998). This notion has not been changed in a more recent consensus on a classification of PPA including the semantic variant, where no EEG markers are reported (Gorno-Tempini et al., 2011). Although a couple of EEG studies were conducted with FTLD patients (Chan et al., 2002, Pijnenburg et al., 2008), little attention has been given to characterize resting EEG markers of SD. The opposite is the case for other dementias, especially for Alzheimer's disease (AD). In particular, numerous studies have found changes in frequency resting state EEG power as compared to other dementias and healthy controls (Rice et al., 1990, Dierks et al., 1993, Ihl et al., 1993, Baiano et al., 2007, Schreiter Gasser et al., 2008).

In recent years, the methods to analyze electrophysiological signals have been profoundly extended. For example, the use of whole scalp electrode montages and thus increasing numbers of sensors has led to what can be referred to as topographical analyses. Topographic relates to its spatial characteristics, that is, changes of the amplitude configuration across electrodes over time. Concretely, a change of topography reflects a transformation of the activation of the neuronal network. In contrast, a shift in amplitude alone indicates that the number of involved neurons firing coherently alters (Koenig et al., 2002). Although topography changes occur in a time range of milliseconds (ms), it has been shown that momentary stable spatial patterns lasting approximately 100 ms can be observed (Lehmann, 1990, Koenig et al., 1999). One possibility to make such discrete, repeatedly appearing topographies or microstates more intelligible are pattern recognition algorithms (Lehmann, 1987). Microstate analyses have been used increasingly to quantify modulations of cognitive processes such as language and memory. For example, in event-related potential (ERP) studies, subtle changes between stimuli conditions of certain tasks (e.g. correct vs. incorrect sentences, related vs. unrelated word pairs) were expressed as differences in microstate onset, offset, duration, number of presence, and topography (Brandeis et al., 1995, Wirth et al., 2007, Grieder et al., 2012). Moreover, microstate

differences were found between patient and control groups in a study that investigated alterations of brain activity in patients with AD and SD (Grieder et al., 2013). These results thus demonstrate that EEG microstate analysis is a powerful tool for disentangling the brain dynamics that are related to external stimuli as well as cognitive disorders.

Furthermore, microstate analyses have served to characterize topographical patterns of the resting state EEG. The majority of the studies have clustered the resting EEG into four microstate classes, which has been found to be the optimal number according to the cross-validation criterion (Pascual-Marqui et al., 1995, Koenig et al., 2002, Britz et al., 2010). With this approach, Van De Ville, Britz and Michel (2010) for instance succeeded to link the microstate classes to the resting state networks obtained with fMRI. Furthermore, Yuan et al. (2012) studied the relationship of simultaneous fMRI and EEG microstate using independent component analysis. Moreover, it has been shown that depending on the sleep stage, the topographies of the microstate classes differ slightly (Brodbeck et al., 2012). Alterations of resting state microstate duration as well as microstate transitions were found in patients with frontotemporal dementia, AD, and schizophrenia as compared to controls (Dierks et al., 1997, Kikuchi et al., 2007, Nishida et al., 2013). However, findings of resting EEG microstates in SD is missing and the notion that the resting EEG in SD is normal has not been investigated further. On the other hand, the literature strongly supports the assumption that if a cognitive state is altered, so should be the microstates. Consequently, one could expect different microstate parameters (e.g. topography, duration etc.) of patients with SD than of healthy controls, as an indication of semantic memory deficits seen in SD.

In accordance with this rationale, the aim of this study was to investigate resting state EEG microstates in patients with SD. One group of healthy elderly (HC) participants and one group of patients with AD served as control groups. We hypothesized that differences in microstates should be expected between SD and HC as well as AD. This assumption is based on the fact firstly that brain atrophy in SD differs from AD, which should lead to altered neuronal generator configurations. Secondly, patients with SD show a more severe semantic memory deficit as

patients with AD, which has been found to alter the topography of ERP microstates in relation to a semantic task (Grieder et al., 2013). However, no specific hypotheses were made on which parameter was expected to be altered in SD compared with the control groups, as no data was available in the literature for this purpose.

## 2. Methods and materials

### 2.1. Subjects

In the current study, 8 patients with semantic dementia (SD), 8 healthy elderly controls (HC), and 8 patients with Alzheimer's disease (AD) were included, while one half of each group was assessed in Osaka, Japan and the other half in Stockholm, Sweden. The main reason for conflating the two-center data was the common difficulty of recruitment of patients with SD due to the low prevalence, difficult diagnosis, and high dropout rate as a consequence of severe cognitive impairment. In order to minimize the risk of age-confounded results, the participant groups were age-matched, because a previous study showed that the mean duration of microstates decreases with age, while the number of microstates per second increases (Koenig et al., 2002). Detailed information about the participants included in this study is provided below.

The study was in accordance with the Declaration of Helsinki and approved by both the Institutional Ethical Review Board of Kansai Medical University, and the Regional Ethics Committee of Stockholm, Sweden. Informed written consent was provided from all participants and their caregivers.

Insert table 1 here

#### 2.1.1. Osaka sample

The participants of Osaka comprised of 4 patients with SD, 4 patients with AD and 4 HC (demography see table 1). The HC were enrolled by advertisement, and their medical history and physical and neurological examination results were normal. All participants were from Osaka in Japan. Patients underwent brain MRI, I<sup>123</sup>-IMP-SPECT and Mini Mental State Examination (MMSE). SD diagnosis was performed in accordance with Lund and Manchester

(1994). The resting EEG was mainly used as clinical diagnosis for excluding epilepsy.

### 2.1.2. Stockholm sample

In accordance with the Osaka sample, 4 patients with SD, 4 patients with AD and 4 HC from Stockholm were included in this study (demography see table 1). The HC were recruited by advertisement and the patients with SD from all over Sweden. SD diagnosis was performed in accordance with the Neary et al. (1998) criteria. Patients with AD were recruited during their treatment at the Memory Clinic of the Geriatric Department at Karolinska University Hospital in Huddinge, Sweden. AD diagnosis was according to the ICD-10 criteria (1992). None of the participants suffered from any other neurological or psychiatric illness nor were they under medication affecting the central nervous system that was not part of their dementia treatment. The resting EEG was not only used for analysis for the purpose of the current study, but also clinically proofed for abnormal patterns such as signs of spikes and waves.

## 2.2. EEG recording

The EEG recording settings differed between Osaka and Stockholm. Therefore, both recording procedures are separately described below. The processing steps that enabled comparison of the data of both recording sites are reported in the EEG preprocessing section.

### 2.2.1. Osaka

After the neuropsychological testing, the participants were asked to sit on a chair located in an electrically shielded room. Resting EEG with eyes closed was recorded from 19 scalp electrodes of the International 10/20 System referenced to linked ear lobes. Vigilance-controlled EEG recording lasted 20 min, with subjects receiving a warning sound when they started to drift towards drowsiness. EEGs were amplified, band-pass-filtered to 0.3-30 Hz, sampled at 200 Hz and stored using the EEG-1100 Nihon Kohden system (Nihon Kohden, Tokyo, Japan). After each EEG recording, 20 artifact-free epochs of 2-s duration each were randomly selected by visual inspection for analysis, excluding eye movements, blinks and drowsiness. The selected data were recomputed against the average reference.

### 2.2.2. Stockholm

Before starting the EEG recording, each participant's medical history was assessed following the neuropsychological testing including the Mini-Mental State Examination (MMSE) amongst others. After this examination, the participants were asked to sit on a chair located in an electrically shielded room. The resting EEG recording in Stockholm was performed using a high-impedance 128-channel HydroCel Geodesic Sensor Net connected to a Net Amps 300 amplifier (Electrical Geodesics, Inc., Eugene, OR, USA). To retain the impedances below 50 k $\Omega$ , the electrodes were soaked in a potassium-chloride solution before being mounted on the participant's head. Recording reference was Cz and ground electrode was placed between CPz and Pz. The sampling rate of 1 kHz was down sampled to 250 Hz. The resting EEG consisted of three periods of eyes closed lasting 2 min each and two periods of eyes opened lasting 20 s each resulting in a total duration of 6 min and 40 s.

### 2.3. EEG preprocessing

For preprocessing, the Vision Analyzer software (Version 1.05, Brain Products GmbH, Gilching, Germany) was used. First, raw EEG data was band pass filtered at 1 – 30 Hz. Next, channels and EEG fragments that were contaminated by infrequent or muscle artifacts were removed by visual inspection. Then, an Independent Component Analysis (Tran et al., 2004) was computed in order to correct for eye movements or repeatedly occurring electrode shifts and electrocardiogram. After that, the average reference of all channels was computed and the previously removed contaminated channels were interpolated (order of splines = 4; maximal degree of Legendre Polynomes = 10; Lambda = 0.00001). Finally, remaining contaminated fragments were deleted with visual inspection.

As a next step, the Stockholm data were adopted to the EEG parameters of the Osaka data. First, the sampling rate was lowered to 200 Hz. Second, the first 20 epochs of 2 s length that were free of any artifacts were extracted and bandpass-filtered to 2-20 Hz. Third, the 19 electrodes which were in accordance with the 19 electrodes recorded at the Osaka site were selected, so that the same electrodes from both recording sites were used for analysis.

### 2.4. Microstate analysis



As outlined in the introduction, EEG microstates are a measure of the well-structured awake resting state of the human brain, which clusters the electrophysiological signal into non-overlapping topographical temporal patterns of synchronized instantaneous neuronal activation. The standard analysis approach was applied in this study which shall be summarized shortly (Lehmann, 1987, Strik et al., 1993, Wackermann et al., 1993). Of the 20 2-second segments all topographies at Global Field Power (GFP) peaks were selected and subjected to a modified k-means spatial cluster analysis (Pascual-Marqui et al., 1995). A number of 4 microstate classes were obtained per participant, which is an adaption from previous studies that recorded for example simultaneous functional MRI-RSN and EEG in normal controls, dementia or schizophrenia (Koenig et al., 1999, Kikuchi et al., 2007, Van de Ville et al., 2010, Brodbeck et al., 2012, Nishida et al., 2013).

Basically, these 4 individual microstate classes were used for two purposes: one was to assign all EEG data points of each participant to the best fitting of the 4 individual microstate classes so that time spans of stable EEG topographies resulted in continuous periods of the same class. A common way to quantify this assignment of is to compute the contribution, occurrence, and duration of each class (Koenig et al., 2005). The contribution indicates how dominant each microstate class is and is thus the ratio in relation to all 4 microstate classes. The occurrence quantifies the count of each microstate class per second. Last, the duration of a period in which a particular microstate class is active reflects the temporal stability of synchronously activated brain regions that contribute most dominantly to the momentary topographical distribution of the EEG signal.

The other purpose of the microstate cluster analysis was the topographical between-group comparisons. In particular, the individual microstate classes (based on the GFP peaks) were permuted to minimize between subject variance and averaged across the members of the participant groups resulting in 4 mean microstate classes for each group. For this procedure, the permutation algorithm described in Koenig et al. (1999) was used. The same algorithm was further applied to assign the AD and SD mean microstate classes in the best fitting way to the 4

HC mean microstate classes in order to enable between-group comparisons of each microstate class. Using a linear regression model for each channel and microstate class, all individual and group-mean microstate classes were corrected for normal aging in order to rule out any outcome confounded by mere age effects. Finally, all individual microstate classes were subsequently assigned to the corresponding group mean microstate classes. To sum up, this procedure structured the individual microstate classes as well as the group mean microstate classes in the way that all microstate classes were classified to one of the common labels A to D. Only through these assignment steps, statistical test of microstate topographies were possible.

### 2.5. Microstate statistics

Individual microstate topographies of each class were compared between groups using the topographic ANOVA (TANOVA) (Strik et al., 1998), as implemented in the Ragu software (Koenig et al., 2011). The TANOVA is a non-parametric randomization test detecting reference and GFP-independent topographic differences between two or more maps (Murray et al., 2008). More detailed, the individual 4 microstate classes per participant, retrieved from the above described cluster analysis, were compared across groups yielding eventual significant topographic differences of microstate classes A-D between HC, AD, and SD. The  $p$ -threshold was set to 0.05 and 5,000 randomization runs were computed. In case of significant group effects, post-hoc TANOVA were conducted in order to obtain the effects in a group-by-group fashion (i.e. SD vs. HC, SD vs. AD, HC vs. AD). In order to assess group differences of microstate contribution, occurrence, and duration, a multivariate analysis of variance (MANOVA) was performed. Moreover, a possible relationship of topographic alteration of microstate classes and cognitive ability was investigated performing bivariate Pearson correlation analysis.

## 3. Results

### 3.1. Microstate analysis

The microstate  $k$ -means clustering analysis yielded four individual microstate classes as illustrated in figure 1 on the left side. Moreover, group mean microstate maps are depicted on the right side of figure 1.

Insert figure 1 here

### 3.2. Microstate statistics

The TANOVA including all three participant groups yielded significant group effects for microstate class B and C (see figure 1 on the right side). Topographies of microstate classes A and D did not differ between the groups. Post-hoc TANOVAs for microstate class B and C showed that SD differed from HC and AD, but no difference was found between the two control groups HC and AD. Following these findings, the Pearson analysis was performed using individual MMSE total score as well as the MMSE language score for bivariate correlation with the aberrant microstate class B (named from here on as microstate class E) found in SD. The results showed that the presence of this microstate class E instead of B was associated with lower MMSE total ( $r = -0.58$ ;  $p$  [two-sided]  $< 0.01$ ) and MMSE language ( $r = -0.56$ ;  $p$  [two-sided]  $< 0.01$ ) scores. The MANOVA assessing microstate group differences of occurrence, contribution and duration yielded no significant results.

### 4. Discussion

The current study is the first that revealed deviations in resting EEG in semantic dementia. Consequently, the notion that resting EEG is normal in semantic dementia has to be revised. In particular, patients with semantic dementia showed altered resting state microstate topographies in class B and C, as compared with a healthy and an Alzheimer's disease control group.

We hypothesized altered microstate classes in semantic dementia due to the deteriorated neurophysiology that leads to semantic memory deficits and thus to an altered state. This rather liberal assumption, due to a lack of existing evidence, proved to be verified by the finding of changed microstate classes B and C topographies. In contrast, microstate classes A and D were comparable between all groups. While this observation is also new for the SD group, the microstate classes of the AD and HC groups were replicated in comparison with previous reports (Koenig et al., 2002, Britz et al., 2010, Brodbeck et al., 2012, Nishida et al., 2013). Although these

findings appear straightforward on first sight, a closer look to the individual and group data demand a more refined interpretation of the results.

Generally, differing microstate topographies mirror distinct neuronal networks and thus reflect different cognitive processes or mental states. Following this, our results indicated that patients with SD showed altered processes found in microstate classes B and C. On the other hand, the comparable microstate classes A and D with the control groups favored the view that some other cognitive processes remain stable. In addition, a significant correlation of lower MMSE scores with the presence of the particular microstate class E was detected. This finding indicated that the reduced general cognitive and language abilities observed in the patients with SD might be manifested by microstate class E suppressing the common microstate class B (or C respectively, as elaborated below). This is in line with previous studies that showed that the microstate analysis is a sensitive tool to disentangle distinct mental states between healthy participants and patients (Koenig et al., 1999, Kikuchi et al., 2007, Nishida et al., 2013). Moreover, the current results correspond with the clinical observation of a distinct symptomatology in semantic dementia rather than a general cognitive deficit (Snowden et al., 1992, Hodges, 2001). In other words, semantic dementia is characterized by an isolated semantic memory deficit (best reflected in the MMSE language score of the available data) while other cognitive functions remain intact. A similar pattern was found in the microstate analysis: microstate classes B and C were altered in semantic dementia, but classes A and D were comparable with those of the controls.

Yet we consider it as important to pinpoint to the very shape of the microstate classes in this study. If one compares microstate classes A to D in the two control groups with the microstate classes of earlier studies, it becomes apparent that they match. Focusing on microstate class B in SD revealed either a clockwise or anticlockwise rotation in comparison to the normal class A or B respectively. Alternatively, one could also speculate about a 90-degree-rotation in comparison with normal class C. The latter approach appears convincing when studying class C of SD. It is obvious that this topography matches the one of normal class B.

Taken together, the profound inspection of the microstate topographies indicated that patients with SD showed normal classes A, B, and D, but no normal class C. Naturally, the question arose of why had then the normal class B of the SD group been assigned to class C. An explanation could be found in the algorithm, which assigned the patients' microstate classes in accordance to the healthy classes (see 2.4). As described in Koenig et al. (1999), all possible assignments are permuted until the solution that maximizes explained variance is found. From this perspective, the assignment of SD class C that looks like normal class B appears plausible, because the topography of SD class B was much closer to normal class B than normal class C, while SD class C, although equal to normal class B, was still relatively closer to normal C than SD class B would have been.

Taking these considerations into account, the main finding of this study is that the SD group did not show a normal class C, but instead a different class E that was not found in the two control groups. The topography of this particular microstate class E has a vertical line that divides the opposite polarities between right and left hemisphere. As can be drawn from the individual microstate classes in figure 1, class E appeared in all patients with SD except for patient labeled as SD5. Class E can also be found in individuals of the control groups, as a profound inspection of the data discovered (HC6, AD4, AD5, and AD7; all assigned to class B). Therefore, class E cannot be viewed as a specific microstate that distinguishes patients with SD from patients with AD or healthy controls. On the other hand, one could speculate about its relationship to semantic memory deficits or underlying brain atrophy, which can be found especially in AD as well as to a lower degree in healthy elderly (Du et al., 2007, Irish et al., 2012). Unfortunately, these hypotheses could not be investigated with the current samples, as scores of semantic memory or measures of brain atrophy were not completely available (see also limitations below). However, normal class C has been associated with an insula-cingulate network, as suggested by Britz et al. (2010). Abnormalities in these regions were reported before in SD and FTD (Rosen et al., 2002) and may be related to aberrance of class C, which has been found to correlate with a dysfunction of the salience network (Nishida et al., 2013).

Interestingly, microstate classes A and D were not significantly different in topography between the groups. Class D was most investigated in previous studies and especially in schizophrenia (Koenig et al., 1999, Kikuchi et al., 2007, Kindler et al., 2011). For example, it has been suggested that class D might reflect frontal lobe function. In our study, fitting parameters and topography of class D were comparable between the groups and previous studies, which indicates that patients with SD do not have a distinct frontal lobe dysfunction from an electrophysiological view. In addition, Kikuchi et al. (2011) showed that panic disorder patient had decreased duration and contribution of class A, which indicated a correlation of class A with anxiety. In the current study, patients with SD evinced a normal class A, both topographically and in terms of the fitting parameters. Moreover, the microstate duration and occurrence was not changed in either of the patient groups in any of the microstate classes. For the AD group, this finding is concurrent with those of Nishida et al. (2013), who did not find any altered microstate duration or occurrence in AD compared to controls. They only found an altered duration of class C in the FTD group, which is not comparable with one of the groups in this study. One can only speculate about the reason of why there were no fitting parameter effects in the present study. Since group differences were only found in the topographical domain, one might argue that neuronal atrophy leads to an altered configuration of active generators, while the frequency and duration of the quasi-stable states remain unchanged. Thus, the particular microstate class E found mostly in SD might be the original but missing class C with an altered topography. In other words, in SD (and possibly the other subjects with class E), microstate class C might have undergone a topographical change due to atrophy or cognitive deficits without alteration of the proportions in duration and occurrence of the four microstate classes. Taken together, the review of these previous studies together with the results of our study implies that abnormality of class C topography might be a peculiarity which characterizes the EEG microstates of patients with SD. Following this, an opportunity to complement an attempt to predict SD based on resting-state EEG microstates could be to additionally collect N400-ERP-data of semantic priming. Grieder et al. (2013) showed recently that an altered N400-

topography separated well between healthy controls and patients with SD or AD. Although this ERP-marker was not specific for SD alone, a deviant N400-topography together with the presence of resting-state EEG microstate class E (instead of microstate class C) might ameliorate the diagnosis of SD.

As already addressed in several sections of this paper, some limitations accompanying this study are mentioned here. Unfortunately, precise measures of semantic memory deficits such as word fluency and word naming were not available for all participants included in this study. This drawback limited a profound interpretation of the microstate results and made it impossible to infer from the electrophysiological data to the symptomatology. Another constraint was the lack of comparable MRI data, which could have provided insight into the relationship of brain atrophy and altered microstate topography. Even though all patients were diagnosed by MR or CT images, the scanning conditions diverged and were thus not included in this study. Finally, despite the attempt to enlarge the sample size by conflating data from two study centers, the number of semantic dementia patients remained relatively small.

To sum up, the current study discovered the appearance of a microstate in a group of patients with semantic dementia that was not part of the common four resting state microstate classes found in the control groups. Although this so-called class E was detected sporadically in patients with Alzheimer's disease and healthy elderly, the significant correlation with the MMSE scores indicated a relationship of the presence of this abnormal microstate with the cognitive deterioration observed in patients with semantic dementia. It remains yet to be determined whether this particular microstate is associated with a specific deficit such as semantic memory impairment or a rather global marker for cognitive decline. Therefore, further investigations comparing resting state microstates with anatomical data and refined neuropsychological scores are needed in order to obtain a distinct picture of the interplay between resting state EEG topographies and the underlying neuronal basis.

Conflict of interest

The authors declare that there is no conflict of interest associated with this study.

#### Acknowledgments

We thank Raffaella Crinelli for performing recruitment and neuropsychological assessment, Francisco Lacerda and Petter Kallioinen of the Department of Linguistics, Stockholm University, Stockholm, Sweden, for their support at the EEG lab. This study was supported by the Swiss Synapsis Foundation and the Swedish Alzheimerfonden.

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## References

- Baiano M, David A, Versace A, Churchill R, Balestrieri M, Brambilla P. Anterior cingulate volumes in schizophrenia: a systematic review and a meta-analysis of MRI studies. *Schizophr Res*. 2007;93:1-12.
- Brambati SM, Rankin KP, Narvid J, Seeley WW, Dean D, Rosen HJ, et al. Atrophy progression in semantic dementia with asymmetric temporal involvement: A tensor-based morphometry study. *Neurobiol Aging*. 2009;30:103-11.
- Brandeis D, Lehmann D, Michel CM, Mingrone W. Mapping event-related brain potential microstates to sentence endings. *Brain Topogr*. 1995;8:145-59.
- Britz J, Van De Ville D, Michel CM. BOLD correlates of EEG topography reveal rapid resting-state network dynamics. *Neuroimage*. 2010;52:1162-70.
- Brodbeck V, Kuhn A, von Wegner F, Morzelewski A, Tagliazucchi E, Borisov S, et al. EEG microstates of wakefulness and NREM sleep. *Neuroimage*. 2012;62:2129-39.
- Chan D, Fox N, Rossor M. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology*. 2002;58:838-8.
- Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. *J Neurol Neurosurg Psychiatry*. 1994;57:416-8.
- Diehl J, Grimmer T, Drzezga A, Riemenschneider M, Forstl H, Kurz A. Cerebral metabolic patterns at early stages of frontotemporal dementia and semantic dementia. A PET study. *Neurobiol Aging*. 2004;25:1051-6.
- Dierks T, Ihl R, Frolich L, Maurer K. Dementia of the Alzheimer-Type - Effects on the Spontaneous Eeg Described by Dipole Sources. *Psychiat Res-Neuroim*. 1993;50:151-62.
- Dierks T, Jelic V, Julin P, Maurer K, Wahlund LO, Almkvist O, et al. EEG-microstates in mild memory impairment and Alzheimer's disease: Possible association with disturbed information processing. *J Neural Transm*. 1997;104:483-95.
- Du A, Schuff N, Kramer J, Rosen H, Gorno-Tempini M, Rankin K, et al. Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. *Brain*. 2007;130:1159-66.
- Galton CJ, Patterson K, Graham K, Lambon-Ralph MA, Williams G, Antoun N, et al. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. *Neurology*. 2001;57:216-25.
- Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, et al. Classification of primary progressive aphasia and its variants. *Neurology*. 2011;76:1006-14.
- Gorno-Tempini ML, Rankin KP, Woolley JD, Rosen HJ, Phengrasamy L, Miller BL. Cognitive and behavioral profile in a case of right anterior temporal lobe neurodegeneration. *Cortex*. 2004;40:631-44.
- Grieder M, Crinelli RM, Jann K, Federspiel A, Wirth M, Koenig T, et al. Correlation between topographic N400 anomalies and reduced cerebral blood flow in the anterior temporal lobes of patients with dementia. *J Alzheimers Dis*. 2013;36:711-31.
- Grieder M, Crinelli RM, Koenig T, Wahlund LO, Dierks T, Wirth M. Electrophysiological and behavioral correlates of stable automatic semantic retrieval in aging. *Neuropsychologia*. 2012;50:160-71.
- Hodges JR. Frontotemporal dementia (Pick's disease): clinical features and assessment. *Neurology*. 2001;56:S6-10.
- Ihl R, Dierks T, Froelich L, Martin EM, Maurer K. Segmentation of the spontaneous EEG in dementia of the Alzheimer type. *Neuropsychobiology*. 1993;27:231-6.
- Irish M, Addis DR, Hodges JR, Piguet O. Considering the role of semantic memory in episodic future thinking: evidence from semantic dementia. *Brain*. 2012;135:2178-91.
- Kikuchi M, Koenig T, Munesue T, Hanaoka A, Strik W, Dierks T, et al. EEG microstate analysis in drug-naive patients with panic disorder. *PLoS One*. 2011;6:e22912.
- Kikuchi M, Koenig T, Wada Y, Higashima M, Koshino Y, Strik W, et al. Native EEG and treatment effects in neuroleptic-naive schizophrenic patients: time and frequency domain approaches. *Schizophr Res*. 2007;97:163-72.

- Kindler J, Hubl D, Strik WK, Dierks T, Koenig T. Resting-state EEG in schizophrenia: auditory verbal hallucinations are related to shortening of specific microstates. *Clin Neurophysiol.* 2011;122:1179-82.
- Koenig T, Kottlow M, Stein M, Melie-Garcia L. Ragu: A Free Tool for the Analysis of EEG and MEG Event-Related Scalp Field Data Using Global Randomization Statistics. *Comput Intell Neurosci.* 2011;2011:1-14.
- Koenig T, Lehmann D, Merlo MC, Kochi K, Hell D, Koukkou M. A deviant EEG brain microstate in acute, neuroleptic-naive schizophrenics at rest. *Eur Arch Psychiatry Clin Neurosci.* 1999;249:205-11.
- Koenig T, Melie-Garcia L. Statistical analysis of multichannel scalp field data. In: Michel CM, Koenig T, Brandeis D, Gianotti LRR, Ackermann J, editors. *Electrical Neuroimaging.* New York: Cambridge University Press; 2009. p. 169-190.
- Koenig T, Prichep L, Lehmann D, Sosa PV, Braeker E, Kleinlogel H, et al. Millisecond by millisecond, year by year: normative EEG microstates and developmental stages. *Neuroimage.* 2002;16:41-8.
- Koenig T, Studer D, Hubl D, Melie L, Strik WK. Brain connectivity at different time-scales measured with EEG. *Philos Trans R Soc Lond B Biol Sci.* 2005;360:1015-23.
- Lehmann D. Spatial EEG Data and Brain Functional-States. *Int J Neurosci.* 1987;32:863.
- Lehmann D. Brain Electric Microstates and Cognition: The Atoms of Thought. In: John ER, Harmony T, Prichep L, Valdes-Sosa M, Valdes-Sosa P, editors. *Machinery of the Mind.* Boston: Birkhäuser Boston; 1990. p. 209-24.
- Murray MM, Brunet D, Michel CM. Topographic ERP analyses: a step-by-step tutorial review. *Brain Topogr.* 2008;20:249-64.
- Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology.* 1998;51:1546-54.
- Nishida K, Morishima Y, Yoshimura M, Isotani T, Irisawa S, Jann K, et al. EEG microstates associated with salience and frontoparietal networks in frontotemporal dementia, schizophrenia and Alzheimer's disease. *Clin Neurophysiol.* 2013;124:1106-14.
- Pascual-Marqui RD, Michel CM, Lehmann D. Segmentation of brain electrical activity into microstates: model estimation and validation. *IEEE Trans Biomed Eng.* 1995;42:658-65.
- Pijnenburg YA, Strijers RL, Made YV, van der Flier WM, Scheltens P, Stam CJ. Investigation of resting-state EEG functional connectivity in frontotemporal lobar degeneration. *Clin Neurophysiol.* 2008;119:1732-8.
- Rankin KP, Kramer JH, Miller BL. Patterns of cognitive and emotional empathy in frontotemporal lobar degeneration. *Cogn Behav Neurol.* 2005;18:28-36.
- Rice DM, Buchsbaum MS, Starr A, Auslander L, Hagman J, Evans WJ. Abnormal EEG slow activity in left temporal areas in senile dementia of the Alzheimer type. *J Gerontol.* 1990;45:M145-51.
- Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology.* 2002;58:198-208.
- Schreier Gasser U, Rousson V, Hentschel F, Sattel H, Gasser T. Alzheimer disease versus mixed dementias: an EEG perspective. *Clin Neurophysiol.* 2008;119:2255-9.
- Snowden JS, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psychiatry.* 2001;70:323-32.
- Snowden JS, Neary D, Mann DM, Goulding PJ, Testa HJ. Progressive language disorder due to lobar atrophy. *Ann Neurol.* 1992;31:174-83.
- Strik WK, Fallgatter AJ, Brandeis D, Pascual-Marqui RD. Three-dimensional tomography of event-related potentials during response inhibition: evidence for phasic frontal lobe activation. *Electroencephalogr Clin Neurophysiol.* 1998;108:406-13.
- Strik WK, Lehmann D. Data-determined window size and space-oriented segmentation of spontaneous EEG map series. *Electroencephalogr Clin Neurophysiol.* 1993;87:169-74.

- Tran Y, Craig A, Boord P, Craig D. Using independent component analysis to remove artifact from electroencephalographic measured during stuttered speech. *Med Biol Eng Comput.* 2004;42:627-33.
- Van de Ville D, Britz J, Michel CM. EEG microstate sequences in healthy humans at rest reveal scale-free dynamics. *Proc Natl Acad Sci U S A.* 2010;107:18179-84.
- Wackermann J, Lehmann D, Michel CM, Strik WK. Adaptive segmentation of spontaneous EEG map series into spatially defined microstates. *Int J Psychophysiol.* 1993;14:269-83.
- Wirth M, Horn H, Koenig T, Stein M, Federspiel A, Meier B, et al. Sex differences in semantic processing: event-related brain potentials distinguish between lower and higher order semantic analysis during word reading. *Cereb Cortex.* 2007;17:1987-97.
- Yuan H, Zotev V, Phillips R, Drevets WC, Bodurka J. Spatiotemporal dynamics of the brain at rest -exploring EEG microstates as electrophysiological signatures of BOLD resting state networks. *NeuroImage.* 2012;60:2062-72.

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Table 1. Age and neuropsychological assessment scores.

Group Sample	Semantic Dementia			Healthy Controls			Alzheimer's Disease		
	Osaka	Stockholm	Total	Osaka	Stockholm	Total	Osaka	Stockholm	Total
N	4	4	8	4	4	8	4	4	8
Age	68.0 (5.7)	63.0 (3.7)	65.5 (5.2)	68.3 (5.6)	63.8 (2.2)	66.0 (4.6)	68.8 (5.3)	61.5 (3.1)	65.1 (5.6)
MMSE	12.0 (5.6)	22.3 (5.9)	17.1 (7.6)	28.8 (2.5)	28.3 (1.3)	28.5 (1.9)	21.5 (4.2)	23.3 (3.9)	22.4 (3.9)
MMSElang	2.8 (2.4)	7.0 (2.0)	4.9 (3.0)	8.0	8.0	8.0*	7.8 (0.5)	7.3 (1.0)	7.5 (0.8)
CDS		2.5 (2.0)						2.3 (1.1)	
GDS		3.5 (0.5)						3.3 (0.5)	
BNT		8.7 (8.3)			56.0 (2.4)			43.0 (7.8)	
AF		4.7 (4.5)			29.7 (4.2)			14.0 (2.8)	
VF		8.7 (7.5)			23.2 (3.7)			9.0 (5.2)	
FAB	5.8 (4.0)						12.3 (1.5)		

Mean (Standard Deviation) scores (years of age respectively) are listed. Abbreviations: MMSE = Mini Mental State Examination (max. 30); MMSElang = MMSE language sub-test (max. 8); CDS = Cornell Depression Scale; GDS = Global Deterioration Scale; BNT = Boston Naming Test (max. 60); AF = Animal Fluency; VF = Verb Fluency; FAB = Frontal Assessment Battery (max. 18). \* All healthy controls achieved the maximum score of 8.

### Figure Legend

Figure 1. On the left side of the figure, all 4 microstate class maps are depicted (horizontally) for each participant included in this study (vertically), clustered for each group (HC: healthy controls, SD: semantic dementia, AD: Alzheimer's Disease). The maps reflect the age-corrected topographical distribution obtained from the clustering analysis using GFP-peak data only. The variance which was explained by the individual 4 microstate classes is shown on top of the individual microstate maps. The right side of the figure shows the group mean microstate classes and the significant p-values of the TANOVA analysis over all 3 groups, and for group-by-group comparisons.

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