What happens when nothing happens? An investigation of pauses as a compensatory mechanism in early Alzheimer's disease

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Abstract

Lexical-semantic impairment is one of the earliest symptoms of Alzheimer's disease (AD) and is usually examined by single word processing tasks. During speech production, pauses are often investigated as a hallmark of a patient's lexical-semantic decline. In the current study, we put forward the hypothesis that pauses reflect different processes according to the type of discourse. We believe that lexical and semantic impairment would predict a patient's pause frequency in a picture-based narrative (PBN) while anterograde memory would predict a patient's pause frequency in a memory-based narrative (MBN). To demonstrate this, we recruited 17 early AD patients and 17 matched controls. They underwent a full neuropsychological and language assessment and two narrative production assessments. We compared pause duration and frequency in the AD participants' and healthy controls' PBN and MBN. A multiple regression model was used in each narrative and in each group individually to assess the relationship between cognitive processes and pause frequency. Our results show that participants with AD produced more pauses in the PBN only. The frequency was predicted by semantic fluency performance with which it was positively correlated, contrary to what was expected. In the MBN, pause frequency in the AD participants was positively correlated with and predicted by their memory performance. We then examined the neuroanatomical correlates of pause frequency in the AD participants. Considering the PBN, pause frequency was also positively correlated with the grey matter density of the anterior temporal lobe. These findings suggest that patients use pauses as compensatory mechanisms in the earliest stages of AD. Pauses therefore may reflect the time required for the compensation and the realisation of a weak process depending on the narrative task and should be considered as a positive sign.

Keywords

Alzheimer's disease, narrative production, pauses, compensatory mechanism

Highlights

Early AD patients use pauses differently according to the narrative type.

The frequency of pauses reflects different processes according to the narrative.

Patients use pauses as compensatory mechanisms in the earliest stages of AD.

1. Introduction

1.1. What is a pause?

Speech production is not continuous and contains pauses. Physiological and cognitive reasons, among others, underlie the production of pauses. Due to the composite nature of these phenomena, no consensual definition exists. Some authors only analyse silent pauses (Deschamps & Grosjean, 1972), or fillers (Bortfeld, Leon, Bloom, & Schober, 2001) while others take into account both types of pauses (Maclay & Osgood, 1959). The threshold used to define a pause may also vary. However, most authors agree that pauses inferior to 200 ms usually reflect respiratory features (Morel & Danon-Boileau, 1998) and a threshold from 200 to 250 ms is the most common definition of a pause found in the literature (Zellner, 1994).

In the normal population, there are various explanations for pauses. Although the degree of familiarity between speakers does not influence the pattern of pauses (e.g. Bortfeld, Leon, Bloom, Schober, & Brennan, 2001; Branigan, Lickley, & McKelvie, 1999), these phenomena are influenced by affective states (e.g. increase with anxiety: Mahl, 1956; Rochester, 1973) or cognitive demands. Interestingly enough some authors have shown that pauses may reflect a lexical decision (Beattie & Butterworth, 1979; Maclay & Osgood, 1959) as well as discourse planning. It has been established, for example, that pause frequency increases according to the complexity of the discourse task (Bortfeld, Leon, Bloom, & Schober, 2001; Lickley, 2001) and pauses are most likely to occur at the beginning of an utterance or before long utterances when there is a heavy cognitive load (Corley & Stewart, 2008). One study analysed pauses in relation to neuroimaging data during a picture-based narrative and added substantial evidence of various functions of pauses (Grande et al., 2012). They underline the fact that when pauses reflect the conceptual planning of speech, they could be associated with the activation of the precuneus. On the contrary, pauses that reflect successfully solved word-finding difficulties could be related to the left middle and superior temporal gyri. According to the authors, these activations may reflect the successful executive control required to select a semantic concept and retrieve its corresponding lexical entry.

Considering the fact that Alzheimer's disease (AD) is characterised by different cognitive changes, the pattern and function of pauses is expected to be different. However, most studies focus on lexical-semantic decline, and group together pauses with other phenomena within the analysis of word finding difficulties.

1.2. Pauses in Alzheimer's disease

Lexical-semantic impairment is one of the earliest hallmarks of AD. Many authors aim to investigate patients' lexical-semantic impairment during discourse processing by analysing word-finding difficulties. This term encompasses various phenomena, including pauses, which are believed to reflect anomia during connected-speech. According to Forbes-McKay & Venneri (2005), word-finding difficulties during discourse includes pauses, repetitions and indefinite terms (e.g. 'thing'), and is significantly more frequent in the picture description of AD participants compared to that of healthy elderly subjects. Croisile et al. (1996), who grouped together pauses and indefinite terms, found the same results as Forbes-McKay & Venneri in a similar descriptive task. Other authors focused on picture-based narratives and also found an increase in word-finding difficulties (Ash, Moore, Vesely, & Grossman, 2007; de Lira, Ortiz, Campanha, Bertolucci, & Minett, 2011). Only Ash et al. analysed AD patients' difficulties in relation to their cognitive abilities, and highlighted a negative correlation between word-finding difficulties and two language tasks: confrontation naming and semantic matching.

However, phenomena included within the analysis of word finding difficulties may have different causes. Morel & Danon-Boileau, 1998, recommended the analyses of grammatical words repetitions exclusively to investigate marks of lexical search. Hartsuiker & Notebaert, 2010, in their analyses of disfluency during lexical access difficulty, mentioned that self-corrections and certain repetitions probably occur when the speaker is more error prone, no matter what is the difficulty. Although these studies have been carried out on typical populations, they underline the importance of analysing each phenomenon individually. Regarding AD, pauses have already been analysed as a specific phenomenon and not be grouped with repetitions or indefinite terms. Such analyses are usually based on personal narratives or conversations. For example, Gayraud et al. (2011) compared the context, duration and frequency of pauses. They showed that AD participants produced more silent pauses than healthy controls but that there was no difference regarding the duration of pauses. Regarding the context of pauses, the authors stressed the fact that the patients produced more pauses outside of the usual syntactic boundaries and before words of high lexical frequency. They interpreted these results as a hallmark of the patients' lexical retrieval and planning difficulties. Hoffmann et al. (2010) indicated a significant increase in hesitations in AD, which are negatively correlated with a patient's MMSE score. They arrived at the same conclusion as Gayraud et al. that lexical difficulties explain a patient's pause production. By analysing a personal-narrative based on an ecological anterograde memory assessment, our group found that the AD participants produced more pauses between utterances than healthy controls (Pistono et al., 2016). We attributed this increase to a greater need for recall and planning during specific discourse. Moreover, as we investigated other cognitive abilities in the same participants, we observed a positive correlation between the AD participants' between-utterances pause frequency and their memory capacities. The AD individuals from this study belonged to the prodromal stage of AD. This could suggest that in the earliest stages of AD pauses reflect a compensatory mechanism used to improve discourse planning and memory processing during a personal narrative.

However, we can assume that patients' use of pauses is not exclusively related to their memory impairment. For example, as shown by Grande et al. (2012), pauses related to resolved word-finding difficulties could be correlated with left middle and superior temporal gyri, two key regions that are impaired in AD. In fact, as mentioned by Joubert et al. (2010) in their study on AD, there are three key areas within the semantic network: the anterior temporal lobe which could represent an amodal semantic store, the prefrontal and the temporo-parietal regions that could be involved in the semantic control processes. In their study, they pointed out a decline in naming and semantic memory from the prodromal stage of AD that is correlated with anterior temporal lobe and inferior prefrontal cortex atrophy. Their findings suggest that the patients' impairment may result from a breakdown of semantic knowledge combined with difficulties in the selection, manipulation and retrieval of this knowledge. Since pauses are usually considered as a reflection of these difficulties during the patient's discourse processing, we can presume that word finding difficulties pauses in AD might be due to semantic control difficulties and/or to semantic knowledge breakdown. However, apart from word finding difficulties there might also be a compensatory mechanism in memory-based narratives (Pistono et al., 2016) or associated with other difficulties that are yet to be investigated. Therefore, examining pauses in AD in relation to their cognitive and neuroanatomical correlates seems to be useful to better understand impairments during discourse processing.

1.3. Current study

In the current study, we put forward the hypothesis that pauses would reflect different processes according to the discourse type. This is why we took into account a picture-based narrative (PBN) and a memory-based narrative (MBN). We compared pause duration and pause frequency in participants with AD and healthy controls in both types of narratives. We then focused on pause frequency and set out to find cognitive (i.e. memory or language) predictors of pause frequency in typical aging and early AD during these types of narratives. Finally, we examined the neuroanatomical correlates of the AD participants' pause frequency. For the AD group, we assumed that lexical and semantic impairment would be a predictor of pause frequency in a PBN, while anterograde memory impairment would be a predictor of pause frequency in a MBN. Concerning neuroanatomical regressions in the picture-based narrative, there might be two hypotheses: pauses would be correlated with the patients' temporal anterior atrophy if they are related to a semantic representation impairment or to the prefrontal and temporo-parietal regions if they are a sign of semantic control difficulties. During the memory-based narrative, pause frequency would be correlated with the frontopolar area (BA 10) atrophy, as in our previous work. Regarding controls, we expect negative correlations and memory predictors in the MBN and negative correlations with lexical-semantic tasks in the PBN.

2. Material and Methods

2.1. Participant selection and inclusion

All participants gave their written informed consent. This study was approved by the local Ethics Committee. Participants with early AD over 60 years of age were recruited. They all came from the outpatient memory clinic of the Neurology Department of Toulouse University Hospital (France).

AD participants were selected if they presented with a memory complaint and had no concomitant history of neurological or psychiatric disease. They underwent the following pre-inclusion assessment:

- Pre-inclusion neuropsychological assessment: Autonomy in daily living (Instrumental Activities of Daily Living (IADL), Graf, 2008); Global cognition (Mini Mental State Evaluation (MMSE)); Anterograde verbal memory (Free and Cued Selective Reminding Test (FCSRT, Van der Linden et al., 2004)). Individuals with AD were included if they met the following criteria: IADL <1 and based on the IWG-2 criteria (Dubois et al., 2014): evidence of a gradual and progressive change in memory function reported by patient or informant for more than 6 months and demonstrated by an episodic memory test, and cerebrospinal fluid (CSF) evidence of AD (described below). 11 AD participants had an MMSE $\geq$ 24 and 6 had a score of 18 to 24 and therefore had prodromal to mild cognitive decline.
- Brain MRI: A high resolution anatomical image, using a three dimensional (3D) T1-weighted sequence and a T2-weighted sequence was obtained. Patients with significant white matter hyperintensities on T2-weighted MRI scan (Fazekas score > 2) were excluded.
- Amyloid assessment with cerebrospinal fluid (CSF) analysis by lumbar puncture: CSF biomarker levels of total tau (T-Tau), phospho-tau (P-Tau), Ab_{42} and Ab_{40} were

measured using an ELISA method (Innogenetics, Ghent, Belgium). Innotest Amyloid Tau Index (IATI) was calculated. P-Tau ≥60 pg/ml and IATI ≤ 0.8 were deemed to be suggestive of AD. In case of an ambiguous profile (P-Tau <60 pg/ml or IATI >0.8), we calculated the Ab_{42}/Ab_{40} ratio and a score <0.045 was considered to be compatible with a diagnosis of AD.

Matched healthy control participants were recruited after AD participants. They underwent the same neuropsychological assessment as the AD group. Healthy controls were included if they had no memory complaint and no history of neurological or psychiatric disease. They were excluded if they presented with cognitive impairment (test scores <-1.5 SDs) during the pre- or post-inclusion neuropsychological assessment.

2.2. Post-inclusion assessment

2.2.1. Neuropsychological assessment

All participants underwent a neuropsychological assessment that measured: visual recognition memory (Doors and People test, Baddeley et al., 1994); short term memory and working memory (WAIS-III Digit Span and Backward Digit Span subtest; Wechsler, 1997); simple attention and cognitive flexibility (Trail Making Test A and B, Reitan, 1958); gnosia (Visual Gnosia Evaluation Protocol, Agniel, Joanette, Doyon, & Duchein, 1992); praxis (Mahieux's battery, Mahieux-Laurent, Fabre, Galbrun, Dubrulle, & Moroni, 2008); apathy (Starkstein scale, Starkstein et al., 1992) and depression (Beck Depression Inventory, Beck et al., 1961). Details concerning the variables used for the analysis are displayed in Appendix 2.

2.2.2. Language assessment

Language production and comprehension was assessed using a language battery dedicated to neurodegenerative diseases at an early stage, the GREMOTs (Bézy, Renard, & Pariente, 2016). It takes approximately 2 hours to complete. Details concerning the variables used for the analysis are displayed in Appendix 2. The picture-based narrative was part of this battery.

2.2.3. Narratives

Picture-based narrative: the PBN was part of the language assessment. It follows a classic narrative structure: initial state, complication, event, resolution, final state (Labov & Waletzky, 1967) see Figure 1. With regards to the procedure for the narrative task according to GREMOTs, the participants were given the same instructions: “This is a story depicted in 5 pictures. Tell me the story”. During the task, the experimenter remained neutral and avoided speaking in order to ensure uniform conditions for discourse production.

Memory-based narrative: the MBN was built to follow the same narrative structure as the PBN. It was based on a “real life” event in which subjects experienced stereotyped mini-events during the neuropsychological assessment (i.e. an incidental learning). The clinical objective was to create an anterograde memory task that could be done in the office and during the time of the neuropsychological assessment. The incident involved a mobile phone that rang during the assessment and which did not belong to the experimenter. As a result, the experimenter needed to find out whose phone it was and return it to its owner. It follows the same five stages as the picture-based narrative described in Figure 1.

After a 20-minute interval during which the neuropsychological assessment continued, participants were asked to recall the mini-events with as many details as possible. More precisely, participants were instructed to “recall everything that happened, from the beginning to the end, as if they were telling this story to someone else”. In addition to the free reminder, cued questions were asked about each part of the mini-events. The experimenter only asked questions concerning elements that had not been supplied by the participant during free recall. Forced-choice questions were then asked for the remaining elements. The task was divided into 8 mini-events scored on 2 points according to the accuracy of the event. The creation and quotation of this test was inspired from previous tasks focusing on episodic memories and personal “reliving” (Calvet, 2014; Lemesle, Planton, Pagès, & Pariente, 2017). The grid is available in Appendix 1.

Both narratives were taped with an Olympus digital voice recorder in a quiet soundproof room. During the task, the experimenter remained neutral and avoided speaking to ensure that productions exclusively reflected participants' speech processing and that conditions were uniform for discourse production.

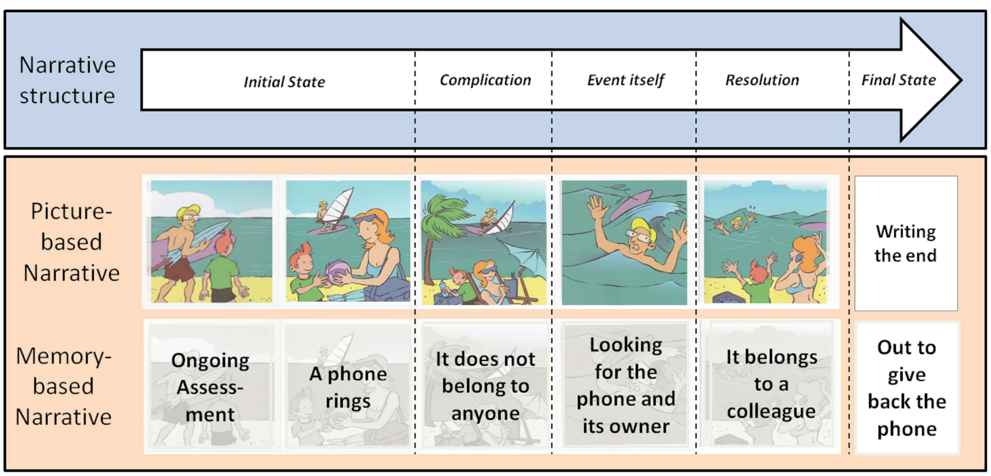


Figure 1: Presentation of the picture-based and the memory-based narratives

2.3. Discourse analysis

2.3.1. Transcribing and coding

The oral productions of participants were recorded and manually and orthographically transcribed with the Child Language Data Exchange System (CHILDES; MacWhinney, 2000) using the embedded Computerised Language Analysis (CLAN) software programme and its CHAT transcription norms.

Concerning transcription of the MBN and the PBN, inter-rater agreement was measured by comparing orthographical transcriptions from two experimenters (one by the author, AP and another by a psycholinguist who was not involved in the study and blinded to group allocation). More precisely, each experimenter first individually transcribed the discourses before comparing both sets of data and resolving any discrepancies until they reached 100% agreement, which was the case for less than 5 utterances. For the subsequent analyses, only AP annotated pauses and lexical content of all PBN and MBN.

For the MBN, the memory score was assessed by two experimenters. Inter-rater reliability was controlled with a Cohen's Kappa. The coefficient was 0.86. This value indicates a strong agreement and assumes data are 64-81% reliable.

2.3.2. Pause analysis

Pause type and length were manually tagged with Praat software (Boersma & Weenink, 2001) using a 200 ms threshold. Various authors agree on the fact that a lower threshold is more likely to reflect respiratory features (e.g. Morel & Danon-Boileau, 1998) and a 200 to 250 ms threshold is the one most commonly found in the literature (Zellner, 1994). This cut-off point of 200 ms was also chosen based on another study on pauses in AD (Gayraud et al., 2011). We included both silent and filled pauses in our analysis.

2.3.3. Variables

The following variables were used to analyse the discourse of both the AD group and the cognitively normal controls:

- Discourse organisation: total number of words in the narrative; total speech duration, speech rate (number of words/total discourse duration, including pauses);
- Lexical content: proportion of closed class and open class words (i.e. nouns, most verbs, adjectives, numerals and adverbs of manner were considered as open class (Ahmed, Haigh, de Jager, & Garrard, 2013)). Standardized indexes were calculated according to the following formula: (Open class – Closed class)/(Open class + Closed class).
- Pauses: pause rate per 100 words; length of pauses (median in ms for each participant)

If multiple pauses were produced one after another, only one was included in the frequency count but durations were added. Moreover, as previously mentioned, the experimenter avoided speaking. However, when they had to respond to a participant's question, pauses by the participant before and/or after were not taken into account. We voluntarily did not analyse the location of pauses, in order to test the hypothesis of a general function of pauses that depends on the narrative task rather than their location within the narrative.

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 20.

2.4.1. Behavioural data

Intergroup comparisons: because some variables are not normally distributed (e.g. pause duration), nonparametric tests were used for intergroup comparisons. The Mann-Whitney U test or Chi-square test was used to measure sociodemographic matching. Comparisons regarding neuropsychological assessment, language assessment and each narrative were made using the Mann-Whitney U test. For significant results, the effect size was assessed using Cohen's d (Cohen, 1992). The results were corrected for multiple comparisons according to Bonferroni's method.

Pearson's correlation: before multiple regressions, we ensured that pause frequency was not inversely related to pause length. Pearson's correlation was used for a more in-depth examination of the link between pause production and lexical processing (i.e. lexical content).

Multiple regression analyses: multiple regression analyses were used to determine the relationship between cognitive variables (predictor variables) and the frequency of pauses in each narrative and each group separately. Regressions were computed to determine R and R2 values. Then, a selection of significantly correlated variables was done to build a stepwise multiple regression model predictive of pause frequency. To do so, pause frequency was used as the dependent variable. Main lexical-semantic as well as anterograde memory tasks from the post-inclusion assessment were chosen as predictors: naming actions, objects and famous faces, semantic fluency and semantic verification, Doors and People Test (set A) and performance during ecological recall (free recall). We also used the number of words as a predictor to ensure that results were not linked to the length of narratives. The absence of potential outliers was controlled by examining Mahalanobis' distance, and Cook's distance. Regressions were motivated by a priori hypotheses. Therefore, corrections for multiple comparisons were not performed.

2.4.2. Neuroimaging data

A high-resolution anatomical image, using a 3D T1-weighted sequence (plane resolution of 1 × 1 mm, slice thickness of 1 mm) was obtained. Grey matter density was assessed using a voxel-based morphometry method on Statistical Parametric Mapping version 12 (SPM 12, Wellcome Trust Centre for Neuroimaging). For each subject, the 3D T1 sequence was segmented to isolate grey matter and white matter partitions, modulated for deformation, normalized to the MNI (Montreal Neurological Institute) space, smoothed (8 × 8 × 8 mm) and pooled by group for statistical analysis.

Correlations between grey matter density and pause frequency were assessed in the patient group using multiple regression (threshold for significance: $p = 0.001$, uncorrected; cluster = 50 voxels).

3. Results

3.1. Population

Seventeen individuals with AD and 17 cognitively normal individuals were included in the study. The AD participants and controls were matched for age (HC=69±5, AD=72.1±2, p=0.28), gender (HC=9Women, AD=10Women, p=0.73) and level of education (in years of education: HC=12.6±3.3, AD=12.4±3.4, p=0.86). The individuals with AD had significantly lower MMSE (HC=28±1, AD=24±3, p<0.0001) and FCSRT scores than the controls (sum of the three free recalls in the FCSRT: HC=32±4.5, AD=8.7±7.7, p<0.0001; sum of the three cued recalls in the FCSRT: HC=46±2.8, AD=23±12, p<0.0001). Regarding the brain MRI, all the AD participants had a Fazekas score < 2. They also all had CSF evidence of AD.

3.2. Neuropsychological and language assessment

During the neuropsychological assessment, the AD participants displayed impairment during the visual recognition memory task (set A: HC=10.8±1, AD=5.9.±3, p <0.0001, d=2.2; set B: HC=7±1.5, AD=3.5.±1.8, p <0.0001; d=2.1). They presented lower visual gnosis capacities (HC=35.2±0.8, AD=30±5, p <0.001, d=1.5). Based on clinical norms, 12 AD participants were below a pathological threshold for the visual recognition task and 4 for the visual gnosis test. The performance of AD participants was also lower for the ecological assessment (free recall: HC=6.4±2.5, AD=3±1.9, p <0.001, d=1.5; free and cued recall: HC=9.4±1.9, AD=5.5±2.8, p <0.001, d=1.6; free, cued and recognition recall: HC=9.4±1.9, AD=6.1±2.8, p <0.001, d=1.4). The other tests (Digit Span, Backward Digit Span, TMT A, TMT B-A, Praxis, Mahieux's battery, Beck and Starkstein) revealed no significant differences between the two groups.

As regards language assessment, the AD participants had lexical impairment during the semantic fluency task (HC=19±4, AD=13±5, p <0.0001, d=2), the famous faces naming task (HC=8±2, AD=4±2, p <0.0001, d=2), the action naming task (HC=33±3, AD=30±3, p <0.001, d=1.1) and semantic verification (HC=17.6±0.7, AD=14.8±1.9, p <0.0001, d=2). Other language components were preserved. Regarding clinical norms, 7 patients were below a pathological threshold for the semantic fluency task; 5 for the action naming task; 5 for the famous faces naming task and 5 for the semantic verification task.

Details of non-significant results from the neuropsychological and language assessments are presented in Appendix 2.

3.3. Intergroup comparisons for both narratives

Picture-based narratives lasted approximately 60 seconds (±20) in the AD group and 48 seconds (±22) in the HC group. During the picture-based narrative, the participants with AD had a significantly lower speech rate, and produced longer and more frequent pauses (Table 1 and Figure 2). As shown in Figure 2, two AD participants can be considered as outliers with a higher pause frequency rate in the PBN. However, results are still significant when these two participants are removed from the group.

AD participants also presented changes in lexical content (higher proportion of closed class words than the healthy controls, Table 1).

Memory-based narratives lasted 78 seconds (±50) in the AD group and 55 seconds (±29) in the HC group. During the memory-based narrative, AD participants had longer pauses than the healthy controls. However, they did not pause more frequently than the control group (Table 1 and Figure 2). They did not produce a higher proportion of closed class words than healthy controls. Statistical results corrected for multiple comparisons are shown in Table 1.

	AD participants	**Healthy Controls**	**p value**	**Cohen's d**
Picture-based narrative				
Number of words	105.47±38.4	117.24±50.2	ns	-
Speech rate	1.83±0.4	2.51±0.78	**p<0.01**	1.1
Pause length (median in ms)	1296.35±720	805.24±342	**p<0.01**	0.87
Pause frequency (per 100 words)	17.25±5.1	12.2±1.84	**p=0.01**	1.32
Lexical content	-0.39±0.14	-0.24±0.1	**p=0.001**	1.23
Memory-based narrative				
Number of words	110.17±38	158.4±73	ns	-
Speech rate	2.04±1.13	3.02±0.64	ns	-
Pause length (median in ms)	855.65±253	629.41±213	**p<0.01**	0.97
Pause frequency (per 100 words)	9.01±3.76	7.41±2.74	ns	-
Lexical content	-0.52±0.06	-0.46±0.07	ns	

Table 1: Intergroup comparisons for the two narratives

Values shown are mean ± SD. Statistically significant results corrected for multiple comparison, are shown in bold.

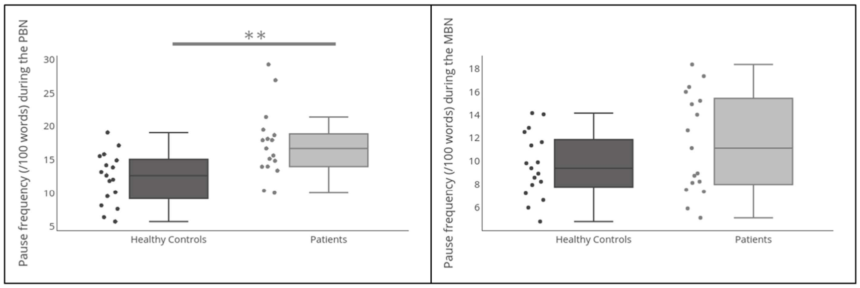


Figure 2: Intergroup comparisons for pause frequency in the PBN (left) and the MBN (right). ** p= 0.01.

3.4. Cognitive predictors of pause frequency

3.4.1. Picture-based narrative

Prior Pearson's correlations showed no negative correlations between pause frequency and pause length in the AD group and a positive correlation in the HC group (AD group: R=-0.29; p=0.6; HC group: R=0.64; p=0.01).

In the AD group, pause frequency was positively correlated with the lexical content index (i.e. proportion of open class words: R= 0.5; p < 0.05) while it was not in the control group (R=0.1; p=0.7).

The first step of multiple regression concerns the correlation between considered variables. As shown in Figure 3, pause frequency in the AD participants was positively correlated with semantic fluency (R =0.55; p =0.01, Figure 3 and Appendix 3). Some of the lexical-semantic tasks were correlated but not highly correlated (>0.9) which means that the model is suitable (Appendix 3).

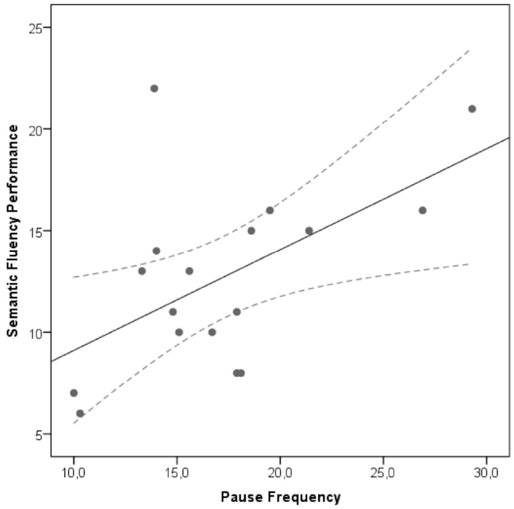


Figure 3: Correlation between pause frequency and semantic fluency performance. The dashed line represents the 95% confidence interval.

The multiple linear stepwise regression model with all variables entered kept one variable for this group. The final model indicates that semantic fluency capacities explained 30.8% of the variance of pauses in the AD group (R=0.55; R^2=0.306; Beta=0.55).

Within the healthy control group, pause frequency during the picture-based narrative was not correlated with any cognitive variables (Appendix 4). Consequently, no stepwise multiple regression was carried out.

3.4.2. Memory-based narrative

Prior Pearson's correlations showed no correlation between pause frequency and pause length in either group (AD group: R=-0.29; p=0.9, HC group: R=0.31; p=0.2).

No correlation was found between pause frequency and lexical content index in the AD (R= -0.04; p=0.9) or control group (R=0.3; p=0.2).

Correlations between considered variables showed that pause frequency in AD participants during the memory-based narrative was positively correlated with their memory performance during the free recall itself (R=0.52, p =0.01) and the Doors and People Test, set A (R=0.68, p =0.001, Figure 4). There were also significant positive correlations between the ecological free recall score and verbal anterograde memory and visual recognition memory (details in Appendix 3).

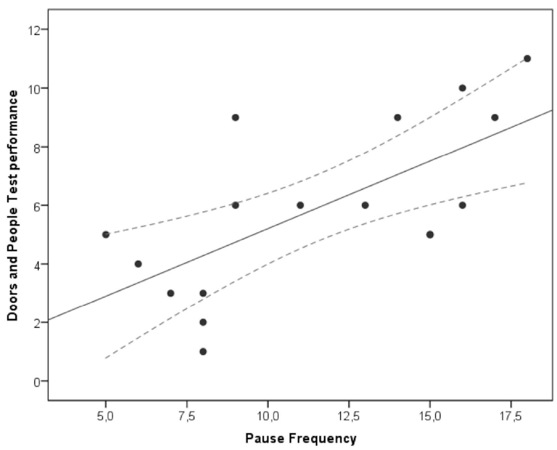


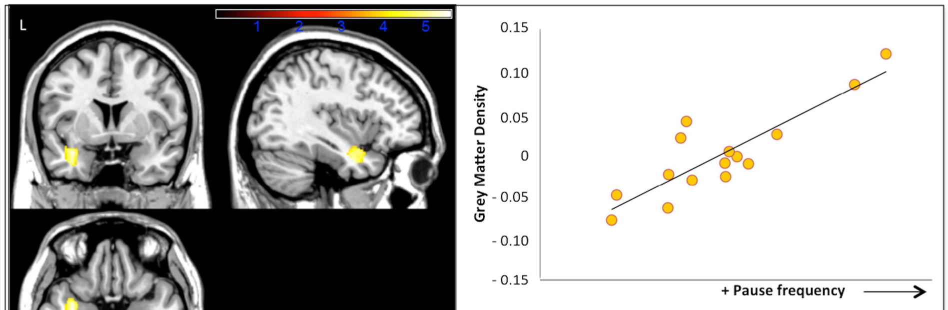
Figure 4: Correlation between pause frequency and the Doors and People Test in the AD group. The dashed line represents the 95% confidence interval.

The multiple linear stepwise regression model with the three memory variables entered, retained one variable: the Doors and People Test, set A. It indicates that this test explained 45.8% of the variance of pauses by the AD subjects (R=0.68; R^2=0.458; Beta=0.68). Within the healthy control group, pause frequency during the memory-based narrative was not correlated with any cognitive variables (Appendix 4). Consequently, no stepwise multiple regression was carried out.

3.5. Neuroanatomical correlates of pause frequency in the AD participants

3.5.1. Picture-based narrative

During the whole brain analyses, we found a positive correlation between pause frequency in the AD participants and their left anterior temporal lobe grey matter (Figure 5).



Brodmann Area	Number of voxels	Coordinates
BA38	K = 474	T = 5.41; x = -36; y = 3; z = -30 T = 4.26; x = -35; y = 0; z = -23

Figure 5: Positive correlation between pause frequency and left BA 38 grey matter density in the AD group.

3.5.2. Memory-based narrative

No correlation was found between the frequency of pauses and grey-matter density in the AD group.

4. Discussion

In the current study, we focused on pause production during a memory-based and a picture-based narrative in early AD. We showed that although the individuals with AD produced the same amount of words as healthy controls in both narratives, they also produced longer pauses. The AD group also produced more pauses in the picture-based narrative. Two different possible functions of pauses were identified according to the narrative type. In fact, pause frequency in the AD participants appeared to be predicted by different cognitive functions, depending on the narrative. Surprisingly, the links between pauses and cognition were positive in both narratives: AD participants who paused more had more preserved abilities regarding processes involved in a narrative task (i.e. lexical-semantic or memory processes). Although current results are in accordance with the previous literature showing an impairment of the temporal organisation of speech in AD (Gayraud et al., 2011; Hoffman et al., 2010), they lead to a new interpretation of pause production in early AD.

4.1. Pauses as a compensatory mechanism used to improve lexical selection

In the picture-based narrative, pause frequency in the AD participants was positively correlated with their semantic fluency scores. Only one study (Ash et al., 2007) made a cognitive correlation with the same type of narrative and found, on the contrary, a negative correlation between word finding difficulties and lexical-semantic tasks. However, as pauses were analysed among other phenomena of word finding difficulties, analyses can lead to other conclusions.

Regarding the present study, we assume that lexical-semantic impairment might actually lead to an increase in pause frequency in early AD, but that this increase should be considered as a sign of lesser impairment. Indeed, the AD group had a lower performance during the oral lexical-semantic tasks of the GREMOTs' battery but the patients with fewer difficulties during the semantic fluency task produced more pauses during their narratives. The frequency of pauses also appeared to be positively correlated with the lexical content of narratives, which was less than the HC group. Using picture-based stimuli, Drummond et al., 2015 found no decline in lexical content in MCI and AD groups. On the other hand, with this measure, Ahmed et al., 2013, showed a linear decline over the progression of AD. The study from

Drummond and colleagues was based on a diagnosis of probable AD that was not based on biological evidence of AD pathology, which might explain the different conclusions.

Stepwise multiple regression reinforced results about semantic fluency capacity, as it was the best predictor of the AD participants' pause frequency in the PBN, explaining around 30% of the variance of pauses. In a study based on primary progressive aphasia, Mack et al., (2015) also found a positive correlation between pauses and lexical-semantic tasks. Indeed, they analysed pauses during the retelling of the story of Cinderella to examine whether pauses would reveal the nature of language decline (i.e. lexical or phonological). Grouping the three variants together, they found a positive correlation, predominantly driven by individuals with a semantic variant, between the pause rate and the naming performance. Similarly, the AD subjects with more severe noun production deficits tended to pause less frequently before nouns during discourse production. Although previous studies argued that confrontation naming imposes minimal demands upon effortful lexical retrieval compared to semantic fluency (Henry, Crawford, & Phillips, 2004), neuroimaging studies have shown that confrontation naming deficits reflected alterations to both temporal and frontal regions, similarly to semantic fluency deficits (Melrose et al., 2009). Our neuroimaging results supports links with semantic processes to explain pause frequency in the AD participants because there was a positive correlation between pause frequency in the AD participants and the temporal pole grey matter density. We can presume that pauses are a mark of an active lexical search supported by more preserved semantic representations: individuals with AD with better semantic fluency and more grey matter density within the anterior temporal lobe produce more pauses while talking during a narrative in which items are constraints.

The anterior temporal lobe is a critical semantic hub (Patterson, Nestor, & Rogers, 2007) and Rogers et al. (2006), suggested that it would be more involved for processing concepts at a subordinate level. Even though it is known that both the left and right anterior temporal lobe regions are crucial for the representation of semantic memory (Lambon Ralph, Cipolotti, Manes, & Patterson, 2010; Tsapkini, Frangakis, & Hillis, 2011), it is a core region of studies based on language tasks. AD. Joubert et al. (2010), for example, found a negative correlation between semantic memory impairment and AD participants' left anterior temporal lobe grey matter volume. Domoto-Reilly, Sapolsky, Brickhouse, & Dickerson (2012), who also focused on early AD, demonstrated that naming impairment was correlated with cortical thinning of the left temporal pole and nearby ventrolateral temporal regions. Since pauses are considered to be a reflection of fluency, naming or semantic memory difficulties during discourse processing, we expected negative correlations between pause production and temporal pole grey matter density. However, this positive correlation is consistent with behavioural results. As previously mentioned regarding the semantic network, the anterior temporal lobe is crucial for semantic representations while the prefrontal and the temporo-parietal regions are essential for the semantic control processes. Current results may signify that pauses in AD are related to the activation of semantic representations.

In a study based on primary progressive aphasia, Mesulam et al. (2013) focused on patients identified on the basis of peak atrophy sites located exclusively or predominantly in the left temporal areas. By characterising naming failures through various tasks, they found that many errors came up from pure lexical retrieval impairment. They also showed that the left anterior temporal lobe is crucial for the integrity of verbal rather than non-verbal representations, selecting verbal labels and managing items specificity. Regarding the current study, we might suppose that the setting up of these processes would necessitate the production of pauses while speaking. In sum, by examining pauses in relation to cognitive and neuroanatomical changes in AD, the current study has different results from the previous literature: contrary to other studies (Croisile et al., 1996; Forbes-McKay & Venneri, 2005), we claim that pauses may not be a negative sign in the AD participants' narratives.

4.2. Pauses as a compensatory mechanism used to improve memory recall

During the memory-based narrative, the AD group did not produce more pauses than healthy controls. Pauses were positively correlated with memory tasks but not with AD participants' lexical content, contrary to the PBN. These results are in line with those of Pistono et al. (2016). It suggests a global function of pauses in this type of narrative that does not depend on their location.

More precisely, in this study, stepwise multiple regressions indicated that visual recognition memory was a predictor of pauses, an explanatory variable that could account for 45.8% of the variance in pause frequency. In other words, better visual recognition memory is predictive of an increase in pauses during a memory-based narrative in early AD. Those memory tasks had already been described as useful in the early detection of AD, since neurofibrillary tangles first appear in the perirhinal cortex, a key structure in visual recognition memory (Barbeau et al., 2004). On the contrary, verbal memory tasks such as the ecological recall might rely on other processes besides memory, and were not retained in the final predictive model of pauses. In other words, both memory variables are positively correlated with pause frequency in this type of narrative, and AD participants with the best memory capacities produced higher rates of pauses, but only the non-verbal memory task could be considered as an explanatory variable. Besides mobilizing more memory resources than the PBN, the MBN may also present less word-retrieval constraints. In fact, this type of production cannot have a uniform content (Bliss & Mccabe, 2006) while picture-based narratives place more demand on vocabulary (Smith, Heuerman, Wilson, & Proctor, 2003). Participants were therefore probably more able to choose alternative words or other strategies in this narrative. This might have also contributed to the results concerning pause frequency in this narrative. No correlation was found between pause frequency and grey matter density. In

Pistono et al. (2016), the use of between-utterance pauses was negatively correlated with the AD participants' frontopolar area (BA 10) grey matter density. Results were interpreted according to the gateway hypothesis (Burgess, Simons, Dumontheil, & Gilbert, 2004). According to this hypothesis, attention is continuously switched between internal and external processing when performing a task. Pauses between utterance were interpreted as reflecting a gateway between inner life (i.e., mental time travel, recall planning) and the outside world (i.e., current recall situation). With regards to this study, we can assume that the short length of the event and the narratives explain why the participants were less inclined to use those gateways and rely on the integrity of this brain region.

4.3. Pauses in Healthy Controls

In the control group, and contrary to our hypotheses, there were no significant correlations. This is not surprising for the picture-based narrative. We can assume that, in this type of narrative and in a normal population with no significant impairment, pauses may reflect many different processes and not just lexical ones (i.e. planning processing as mentioned by Goldman-Eisler, 1968, and/or conceptual processing as in Grande et al., 2012). On the contrary, like Pistono et al. (2016), we expected negative correlations in memory-based narrative. We think that the lack of results is partly due to the ecological memory task used in this study, which is easier than the one used in the Pistono et al. (2016) study. The fact that controls had better speech rates and a higher number of words in the MBN might prove that this task was easier than the PBN for healthy participants, probably because it represents a more everyday task. Smith et al. (2003) compared various discourses in young participants and also found that participants were more productive during a personal narrative than during a picture description task. Moreover, the memory tests used in the assessment presented a ceiling effect in this group, which might explain the absence of correlations. However, this lack of result in the control group also underlines the sensitivity of the task in discriminating early AD from normal aging, as shown by intergroup comparisons for this task. Although it might be easy for healthy controls, and this is therefore reflected in their real-life communication, AD participants experience difficulties and the amount of pauses might bring information about this impairment.

4.5. Strength and Limitations of the study

Our study could be considered as a proof-of-concept study to stress the importance of the integration of linguistic behaviour together with cognitive and neuroanatomical changes. We especially built a memory-based narrative whose structure had to be close to the clinical picture-based narrative. This is why the experimenter had to follow a rigorous plan during the onset of the event and make sure that the participant was involved in its resolution. Beyond the basic structure, the two narratives are comparable in number of words, which means that it makes sense to draw a parallel between the tasks. It also reinforces the idea that the different functions attributed to pauses are not due to the length of one of the tasks. However, we did not strictly compare the two narratives, especially because we believe that they are not comparable in terms of the processes involved (and as notably shown by the predictors of pause frequency).

Moreover, we paid particular attention to the creation of the memory-based narrative, to ensure that it was grounded on the definition of episodic memory: "*Episodic memory is about happenings in particular places at particular times, or about 'what,' 'where,' and 'when*'" (Tulving, 2002, p.3) Therefore, questions for rating this task were built on these three components (as described as in the Appendices). The assessment was also based on incidental and contextualised events, which is more related to the memory impairment due to AD. Such clinical and ecological memory assessment already exists for other diseases (i.e. epilepsy:

Lemesle et al., 2017; functional amnesia: Tramoni et al., 2009). Regarding psychometrics, it has a good inter-rater agreement; it is positively correlated to other memory tasks (both verbal anterograde memory and visual recognition), and there are significant intergroup differences between controls and AD participants (together with high sizes effects).

As for linguistic analyses, pause investigation presents some limitations, as we did not differentiate silences and hesitations within the analyses. This choice was based on the fact that the AD group produced few hesitations. The analysis of pauses was also carried out by one experimenter, which makes it impossible to measure inter-rater reliability. The use of longer narrative samples would improve pause analyses. Besides increasing the sample of phenomena, it would allow us to investigate the context of pauses (e.g. frequency of the following word, production of semantic paraphasia, revisions etc. similar to Gayraud et al., 2010 or de Lira et al., 2011), and would probably be more sensitive to the distinction between early AD patients and healthy controls. Lastly, these findings are based on a sample of MCI and early AD patients, as indicated by their MMSE. They had limited impairment in the language and neuropsychological assessments. Most of the AD participants were above a pathological threshold for every language test, which might be surprising in comparison to the literature which shows early impairment during semantic fluency tasks or confrontation naming tasks (see Verma & Howard, 2012, for a review) in AD. The object naming task in particular appeared to be non-significantly different between the two groups. Therefore, the question remains of what pattern of pauses and what compensatory mechanisms would occur in a sample of patients with deeper language impairment. Moreover, the mean level of education was relatively high in both groups. This might explain the main result concerning semantic fluency, as increased patient education may lead to a worse semantic fluency performance (Laws, Duncan, & Gale, 2010). It might also justify the controls' good performance for every task.

4.6. Future directions

As previously mentioned, the results from the current study differed from the previous literature, which has concluded that pause production is a mark of deeper impairment (e.g. Ash et al., 2007; Gayraud et al., 2011). Such findings are due to the integration of cognitive and neuroanatomical data in relation to discourse analysis, but they are also probably linked to the sample of patients we recruited. In fact, AD participants from the previous studies belonged to groups with mild to moderate or severe stages of AD (Hoffman et al., 2010; Gayraud et al. 2011), whereas we recruited patients with AD. In the current study, we focused on pause frequency, but the function of pause length should also be considered. However, since variance and normal inter-individual variability in AD patients are important, the parametric statistical methods we used in the current study are not appropriate for this variable. We are currently considering intra-subject analyses, which are more suitable to analyse contexts in which pause length significantly, increase in each individual. This will allow us to investigate the hypothesis that pause length increases with verbal planning demand. Length of utterances might be an important variable to take into account too for the analysis of pauses in general, as the variance of speech rate is known to decrease with longer utterances (Goldman-Eisler, 1954).

The use of pauses may reflect the time required for the compensation and realisation of a weak process. In Pistono et al. (2016), dealing with a personal-based narrative, pauses were associated with memory processes. In the current study, we stress the same conclusions with a shorter memory-based narrative. We also show that, during a picture-based narrative in which lexical-semantic loads are higher, pauses seem to reflect those specific lexical-semantic processes. It now seems crucial to investigate other stages of AD to know until which stage of

AD such mechanisms may be employed. It also remains open whether this strategy may be generalised to other cognitive processes, cognitive tasks or diseases.

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Appendix 1: Memory assessment of the memory-based narrative

	Free Recall Mandatory elements	**Scoring**	**If 0 during the Free Recall: Cued Recall**	**Scoring**	**If 0 during both the Cued Recall: Recognition**	**Scoring**
What	A phone rang	/2	What noise did we hear?	/1	A phone / A clock	/1
	The experimenter wondered what was happening	/2	What was my reaction?	/1	I was surprised / I was expecting a phone call	/1
	The experimenter used the phone to call the last number and find the owner of the phone	/2	What did I say on the phone?	/1	I asked who the person wanted to talk to using this number/ I asked for information about the hospital	/1
Where	The phone was in the lab coat	/2	Where did the phone come from?	/1	A lab coat / a drawer	/1
	The experimenter went out to give the phone back to the owner	/2	Where did I go?	/1	To my colleague's office / To the hospital reception	/1
When	When during the assessment	/2	When did it happen?	/1	At the beginning of the assessment / when you were answering questionnaires	/1
	Phone call duration	/2	How much time did I spend on the phone?	/1	1min / 10 min	/1
	Period of absence of the experimenter	/2	How long was I gone from the office?	/1	1min / 10 min	/1

Appendix 2: Non-significant results of the post-inclusion neuropsychological and language assessments (Bonferroni corrected)

TMT, Trail Making Test. Values shown are the mean ± SD. 3 patients did not undergo the TMT part B.

	Healthy Controls	**AD participants**	**p value**	**Number of patients below a pathological threshold**
Neuropsychological assessment				
Digit Span	6±1.2	5±1.1	ns	3
Backward Digit Span	4.6±1.4	3.6±1	ns	11
TMT A (time)	39.3±12	72.9±38	ns	4
TMT B-A (time)	47±17	103±64	ns	7
Mahieux's battery (/23)	22.8±0.5	21.6±2.03	ns	2
Beck	1.9±1.8 Min:0;Max:7	3.4±7.3 Min:0;Max:16	ns	1
Starkstein	8.2±4.3 Min:0;Max:17	10.8±5.8 Min:0;Max:20	ns	6
Language assessment				
Fluency, "verbs"	40±14	25±10	ns	3
Fluency, letter "V"	19±7	14±6	ns	5
Naming, Objects (/36)	34±1	31±3	ns	3
Semantic verification (written) (/18)	17.3±1	14.7±3	ns	3
Syntactic comprehension (/24)	21.7±2	19±3	ns	3
Sentence production (/6)	6±0.2	5.2±1	ns	0
Order execution (/6)	6±0	5.6±0.6	ns	1
Text comprehension (/3)	2.9±0.2	2.5±0.9	ns	2
Repetition, word (/10)	9.9±0.3	9.5±1	ns	1
Repetition, sentence (/4)	3.9±0.2	3.5±0.8	ns	1
Reading, word (/30)	29.5±0.6	29.4±0.8	ns	2
Reading, non-word (/15)	14.6±0.7	14.1±1	ns	1

Dictation, single words (/12)	11.2±0.8	10.5±2.1	ns	1
Dictation, non-words (/6)	5.4±0.6	5.7±0.5	ns	0
Dictation, sentences (/27)	25.3±2.1	25±1.8	ns	0

Appendix 3: Correlations between the cognitive variables in the AD group, a first mandatory step for multiple regressions

	Pause frequency MBN	Pause frequency PBN	Semantic Fluency	Action naming	Naming famous faces	Object Naming	Semantic verification	Ecological free recall	Doors and People Test, set A
Pause frequency MBN	-	-	r =0.24 p =0.2	r =0.04 p =0.4	r =-0.11 p =0.34	r =0.03 p =0.5	r =-0.18 p =0.2	**r =0.52** **p <0.05**	**r =0.68** **p =0.01**
Pause frequency PBN	-	-	**r =0.56** **p =0.01**	r =0.06 p =0.4	r =-0.11 p =0.3	r =0.27 p =0.1	r =0.2 p =0.2	r =-0.02 p =0.5	r =0.26 p =0.2
Semantic Fluency	-	-	-	**r =0.53** **p <0.05**	**r =0.41** **p =0.05**	r =0.35 p =0.08	r =0.03 p =0.5	r =0.39 p =0.06	r =0.24 p =0.2
Action Naming	-	-	-	-	r =0.41 p =0.06	**r =0.58** **p <0.01**	**r =0.56** **p =0.01**	r =0.32 p =01	r =0.33 p =0.1
Naming famous faces	-	-	-	-	-	r =0.39 p =0.06	r =0.34 p =0.09	r =0.21 p =0.2	r =-0.12 p =0.32
Object Naming	-	-	-	-	-	-	**r =0.49** **p <0.05**	r =0.18 p =0.2	r =0.27 p =0.1
Semantic verification	-	-	-	-	-	-	-	r =-0.16 p =0.3	r =-0.11 p =0.2
Ecological free recall	-	-	-	-	-	-	-	-	**r =0.51** **p <0.05**
Doors and People Test, set A	-	-	-	-	-	-	-	-	-

Appendix 4: Correlations between the variables used for multiple regressions in the control group

	Pause frequency MBN	Pause frequency PBN	Doors and People Test, set A	Ecological free recall	Semantic Fluency	Object Naming	Action Naming	Naming famous faces	Semantic verification
Pause frequency MBN	-	-	r =-0.31 p =0.2	r =0.06 p =0.8	r =-0.12 p =0.6	r =-0.03 p =0.9	r =0.067 p =0.8	r =-0.17 p =0.5	r =-0.19 p =0.5
Pause frequency PBN	-	-	r =-0.33 p =0.2	r =0.23 p =0.4	r =-0.05 p =0.8	r =-0.28 p =0.2	r =0.36 p =0.2	r =-0.20 p =0.4	r =-0.08 p =0.8
Doors and People Test. set A	-	-	-	r =-0.17 p =0.5	r =-0.24 p =0.5	r =0.02 p =0.9	r =-0.47 p =0.1	r =0.02 p =1	r =-0.11 p =0.7
Ecological free recall	-	-	-	-	r =0.17 p =0.5	r =0.18 p =0.4	r =0.28 p =0.3	r =0.29 p =0.3	r =0.3 p =0.2
Semantic Fluency	-	-	-	-	-	r =0.4 p =0.1	**r =0.6** **p =0.01**	r =0.35 p =0.2	r =0.46 p =0.1
Object Naming	-	-	-	-	-	-	r =0.21 p =0.4	r =0.06 p =0.8	**r =0.54** **p <0.05**
Action Naming	-	-	-	-	-	-	-	r =0.47 p =0.1	**r =0.6** **p =0.01**
Naming famous faces	-	-	-	-	-	-	-	-	**r =0.67** **p <0.01**
Semantic verification	-	-	-	-	-	-	-	-	-