Name of the researcher	Frédéric Peters
Selection Year	2012
Host institution	University of Liège
Supervisor	Steve Majerus
Period covered by this report	from 01/10/2014 to 30/09/2015
Title of the project	THE CONTRIBUTION OF EXECUTIVE CONTROL PROCESSES TO LEXICO-SEMANTIC IMPAIRMENT IN ALZHEIMER'S DISEASE AND SEMANTIC DEMENTIA

1. Objectives of the proposal (1 page)

The main purpose of this project was to further characterize deficits at the lexical and semantic levels of language processing in Alzheimer's disease (AD). Although a great deal of research has been devoted to the study of language processing as such in AD, the role of executive control processes in language processing impairment have not yet been investigated. This is an important question, since deficits in executive control are commonly observed in the early stages of AD. Providing an answer to this question will allow for more efficient and targeted language rehabilitation in patients suffering from AD, and hence improve their communicative abilities, which is essential for maintaining AD patients socially integrated. From a diagnostic point of view, it is also of fundamental importance to explore this question, as deficits of semantic control processes may help to distinguish AD patients' semantic impairment from that seen in patients with other neurodegenerative disease, notably patients with semantic dementia who show a progressive deterioration of semantic knowledge but preserved semantic control abilities.

There is considerable evidence that performance on various tasks involving lexico-semantic knowledge, such as naming tasks, are impaired in patients with AD. Much of the controversy surrounding the study of this phenomenon stemmed from the access vs. degradation debate, that is, whether naming impairments in AD result from a progressive degradation of semantic knowledge, similarly to what is seen semantic dementia, or from a more general disruption impairing access to intact representations [1].

In an effort to elucidate this issue, this project included two experiments investigating different executive control mechanisms involved in the processing of semantic knowledge. In the first experiment, two main cognitive functions of semantic control were assessed: (i) the ability to resolve lexico-semantic interference by inhibiting target-related distractors or task-irrelevant meanings of words and (ii) the inhibition of no longer relevant lexico-semantic representations after their selection. In the second experiment, the aim was to specifically address the question of the neural substrates of semantic impairments in AD using functional magnetic resonance imaging (fMRI), and to determine to what extent the brain regions known to be involved in semantic control processes are impaired in AD.

2. Methodology in a nutshell (1 page)

In order to achieve these objectives, the first challenge was to develop relevant tasks for measuring semantic control processes. Two main tasks have been chosen among the different experimental procedures that were piloted. In the first task, semantic interference was manipulated via the need to focus on task-relevant meanings of a given word while ignoring alternative meanings of the same item (homonym interference). Consider the situation in which subjects have to pay attention to a pair of semantically-related probes words (e.g. «bark» and «tree») and to decide between a target word (e.g. «wood») and a distractor word (e.g. dog) which one is related to both probe words (see Figure 1). In addition, the level of semantic interference was manipulated by presenting a word before each trial, either cueing the task-relevant semantic relationship (e.g. «branch») or the probe-distractor relationship (e.g. « noise »). Typically, semantic judgment scores are expected to be better and reaction times faster for task conditions with an unrelated distractor than for task conditions with a highly related distractor. In addition, to determine whether possible executive control deficits in AD were restricted to semantic content or whether these deficits were amodal, the same task procedure was used with nonword stimuli (i.e. phonological judgment task) and with geometrical figures (i.e. visual judgment task).

A second task has been developed to specifically investigate post-selection suppression, that is the ability to inhibit activation of no longer relevant information after it has been selected. Indeed, several models of speech processing assume that lexico-semantic representations are inhibited after they have been processed to prevent their reselection [1,2]. Inhibition deficits at this level may lead to progressive difficulties in naming or identifying multiple, consecutively presented language items. These difficulties are due to an abnormal level of persisting activation of lexico-semantic representations from earlier processed words which interfere with subsequent item processing. Post-selection suppression was examined by measuring the semantic blocking effect in cycling picture naming tasks. In this task, participants had to repeatedly name blocks of pictures (sets of 7 different items) over successive cycles of presentation. Performance for blocks of items belonging to the same semantic category (homogeneous sets) was compared to performance for blocks of items from mixed categories (heterogeneous sets). Typically, the repeated presentation of items leads to a progressive increase in proactive interference, as revealed by slowed naming response times across cycles. Importantly, because members of the same semantic categories are likely to be strongly associated, this effect is usually largest for homogeneous sets of items (semantic blocking effect).

In the first experiment, these two main tasks have been administered together with several control tasks during two testing sessions. Fourteen patients fulfilling diagnostic criteria for probable Alzheimer's disease at a mild stage, 4 patients with semantic dementia and 20 healthy elderly subjects participated to this study.

In the second experiment, the first task we described (semantic judgment task) was adapted for administration in an fMRI environment. The adapted semantic judgment task included different task conditions in which the probe and the distractor words are manipulated to increase, or decrease the level of semantic interference (see figure 1). A phonological judgment task using nonwords was also administered as a control task in order to subtract the brain activity related to sublexical language processing and motor programming from the target brain activity associated with the semantic judgment task.
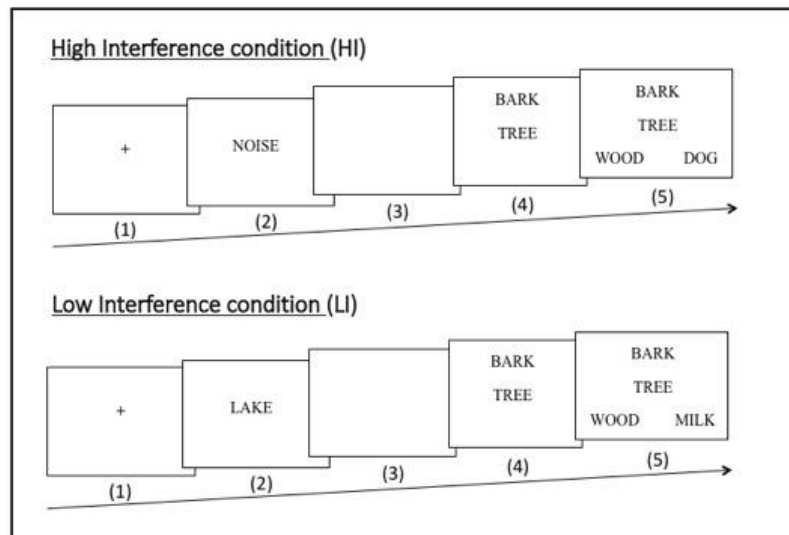
Fig.1. Example of a high interference (HI) trial and a low interference (LI) trial in the semantic judgment task. Display of (1) a fixation cross, (2) a probe word, (3) a blank screen, (4) a reference word pair and (5) a target word (bottom left) and a distractor word (bottom right).

3. Results (8-10 pages)

3.1. Experiment 1

In the first experiment, the same battery of semantic processing tasks was administered to a group of 14 patients with mild Alzheimer's disease (AD), 5 patients with semantic dementia (SD) and a group of 20 healthy elderly controls (CTRL). First, we present the results of group comparison analyses between AD and CTRL groups for the two main tasks. Then, single-case analyses of patients with SD are presented.

Semantic judgment task:

We first conducted statistical analyses (e.g. repeated-measures Anovas) with the percent of correct responses as the dependant variable. As expected, subjects showed a lower proportion of correct responses in the HI condition than in other conditions, and the best performance was obtained in the LI condition. This suggests that the use of distractors related to alternative meanings of the polysemic reference word had a negative impact on subjects' capacity to make the right judgment in this task. Our results also showed that the CTRL group obtained a significantly higher proportion of correct responses than the AD group, indicating semantic judgment deficits in AD patients. More importantly, we found a significant interaction between group and task conditions. Post-hoc analyses showed that the AD patients' deficits increased in conditions with a higher level of semantic interference. This confirms our expectations that semantic control is impaired in AD patients.
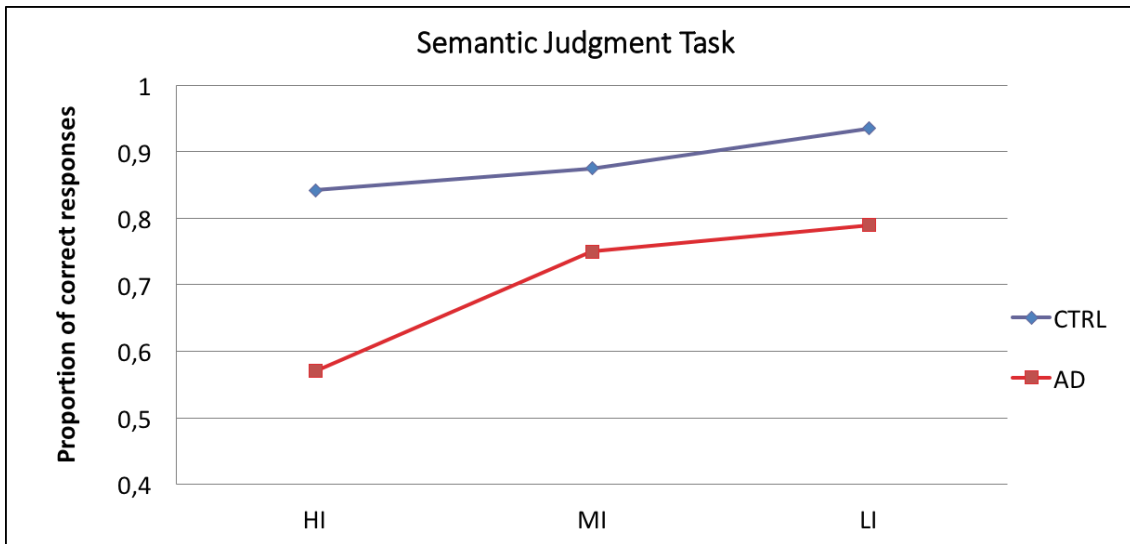
Fig.2. Proportion of correct responses in the semantic judgment task in a group of 14 patients with mild Alzheimer's disease (AD) and 14 healthy elderly control participants (CTRL). Performance are displayed for the High Interference (HI), Mild Interference (MI) and (LI) Low Interference task conditions (LI).

A second analyses was performed on reaction times as a dependant variable. The results showed that reaction times in AD group were significantly slower than in the CTRL group. A significant interaction between group and task conditions was also found. Surprisingly, further post-hoc analyses indicated that mean reaction times were faster in the HI condition than in lower interference conditions for the AD group, whereas in the CTRL group, as expected, reaction times were faster in lower interference conditions than in the HI condition. These results can be interpreted when considering the results on the proportion of correct responses in the AD group. The increase of semantic interference appears to have induced faster but incorrect responses in AD group suggesting that these patients may not be able to inhibit the activation of task-irrelevant meaning of polysemic word due to their semantic control deficits. In contrast, the preserved use of inhibition mechanisms necessary for semantic interference resolution in CTRL subjects leads to the expected slower reaction times.
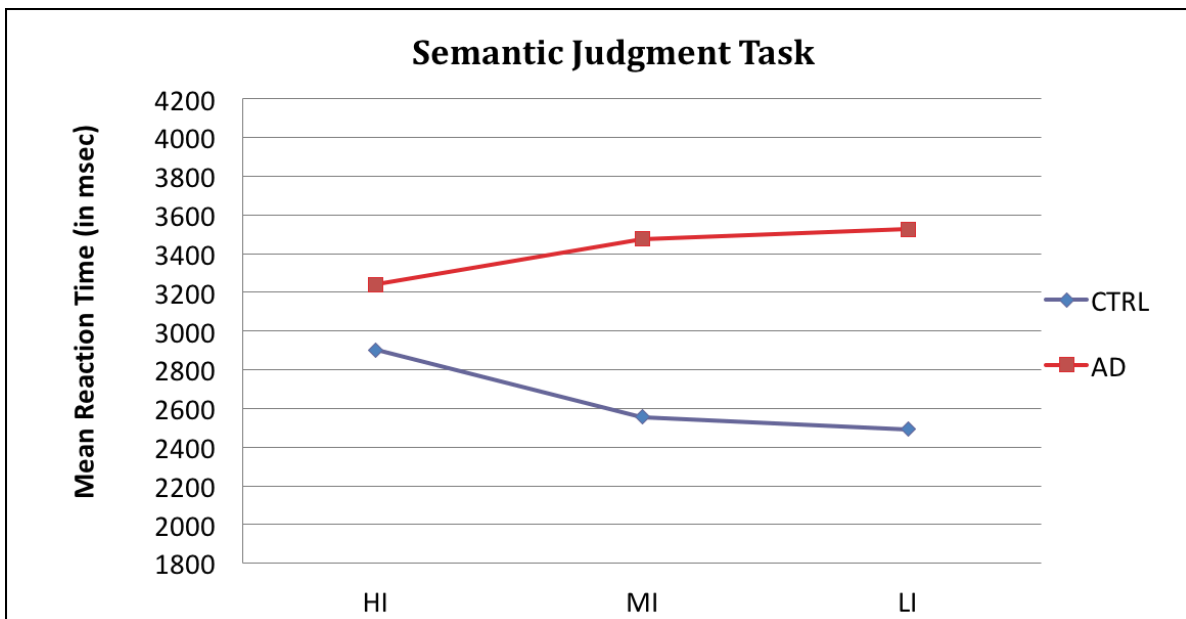
Fig.2. Mean Reaction time in the semantic judgment task in a group of 14 patients with mild Alzheimer's disease (AD) and 14 healthy elderly control participants (CTRL). Performance are displayed for the High Interference (HI), Mild Interference (MI) and (LI) Low Interference task conditions (LI).

Blocked cycling naming task:

For this task, we performed statistical analyses to examine the effect of group (AD vs CTRL), the effect of naming cycles (cycle 1 to 4), the effect of task condition (homogeneous vs heterogeneous set of stimuli), as well as the interaction between these variables. We first conducted analyses on mean reaction time as the dependant measure. Results showed a significant main effect of cycle. Reaction times decreased over the successive presentation cycles. As expected, we also found a significant task condition effect, heterogeneous sets of stimuli being named faster than homogeneous sets of stimuli. A significant interaction between cycles and the type of stimulus sets indicates that repeated presentation of items leads to a progressive increase in proactive interference, particularly for the homogeneous condition. Naming performances for homogeneous sets of items did not significantly improve across cycles, whereas response times progressively decreased from cycle 1 to cycle 4 for heterogeneous sets of items, (semantic blocking effect). Overall, reaction times in the AD group were significantly slower than in the CTRL group, confirming naming difficulties in AD. Most notably, the semantic blocking effect was larger in the AD group than in the CTRL group. This result is in agreement with our main hypothesis that semantic control is impaired in AD, and that inhibition deficits at this level may lead to progressive difficulties in naming or identifying multiple, consecutively presented language items.
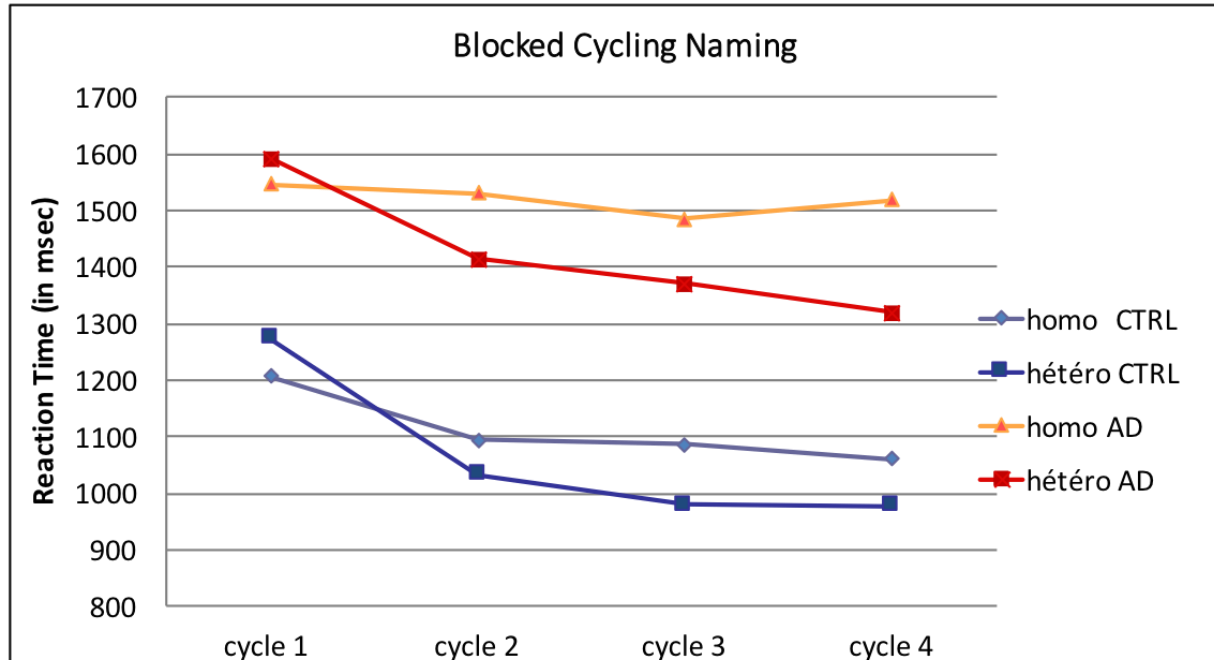

Fig.3. Mean Reaction time in the blocked cycling naming task in a group of 14 patients with mild Alzheimer's disease (AD) and 14 healthy elderly control participants (CTRL) across 4 successive cycles. Performance are displayed for homogeneous blocks and heterogeneous blocks.

Analyses of naming accuracy revealed three main results. First, the AD group produced significantly less correct responses than the CTRL group, confirming general naming deficits in AD patients. Second, we conducted an analysis of errors showing that AD patients produced a greater

proportion of substitution (i.e. naming an item with a word referring to an object previously shown during the task) and intrusion (i.e. naming an item with a word referring to an object not shown during the task) errors. Furthermore, the proportion of substitution errors in the AD group was significantly higher than in the CTRL group only for homogeneous sets of stimuli (see fig. 5). This indicates that substitution errors in AD patients resulted from the higher level of semantic interference when the patients had to successively name stimuli belonging to the same semantic category, and thus inhibit previous activations of target-related stimuli.
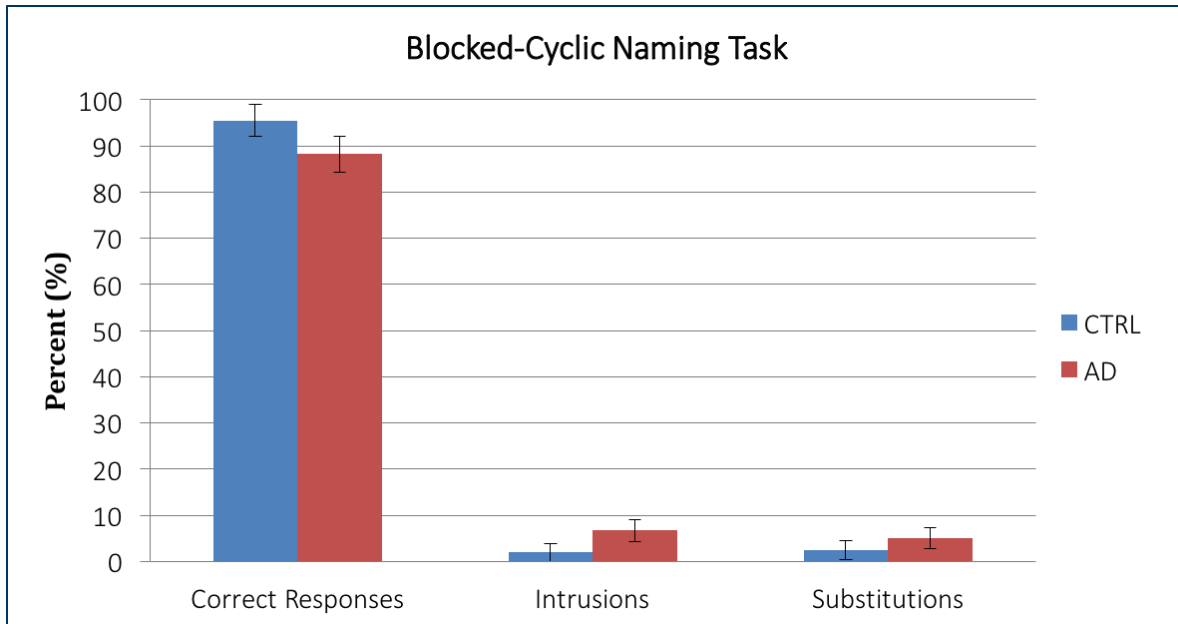

Fig.4. Naming accuracy and proportion of intrusion and substitution errors in the blocked cycling naming task in a group of 14 patients with mild Alzheimer's disease (AD) and 14 healthy elderly control participants (CTRL).
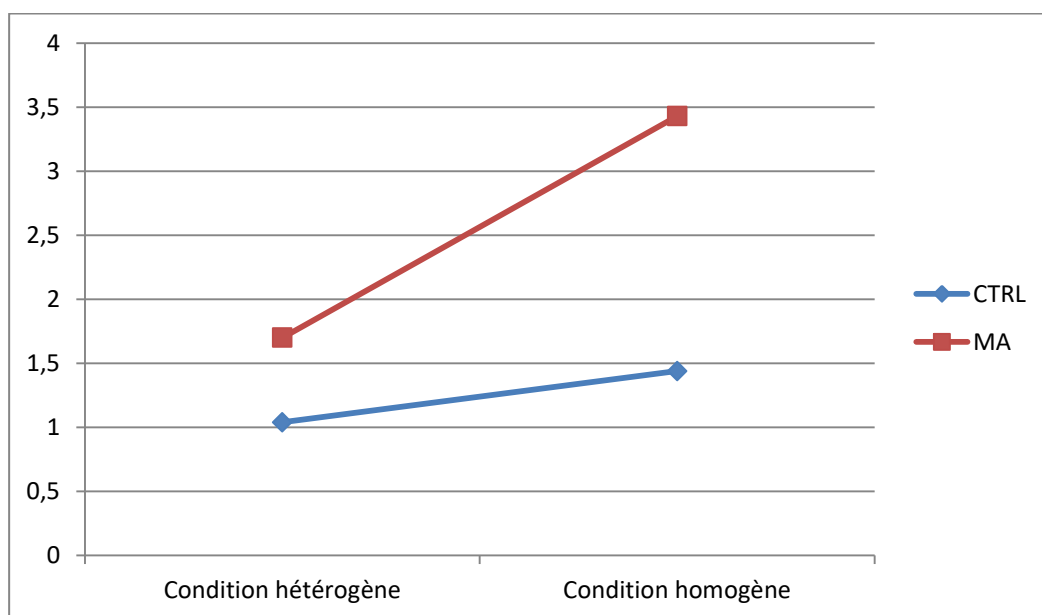

Fig.5. Proportion of substitutions in the blocked cycling naming task in a group of 14 patients with mild Alzheimer's disease (AD) and 14 healthy elderly control participants (CTRL). Performance are displayed for homogeneous blocks and heterogeneous blocks.

Semantic Control in semantic dementia:

The same battery of tasks had been used to examine semantic control in 4 patients with semantic dementia. Because semantic dementia is a very infrequent form of dementia, we adopted a single-case study approach to analyze patients' performance. Each patient with SD was compared to a group of 10 healthy elderly subjects matched for age. According to previous studies by Jefferies and collaborators (1, 2), we anticipated similar semantic interference effects in SD patients as compared to control subjects.

Unfortunately, the loss of semantic knowledge was too severe in one of the four SD patients (EG) so that he could not perform some the tasks. Performance of the 3 remaining patients (OV, AJ and EC) are summarize below for the two main experimental tasks:

- Patient OV: For the semantic judgment task, OV showed a high response accuracy with a similar pattern of performance as the control group (i.e. effect of task conditions: HI<MI<LI). More specifically, the size of the semantic interference effect, as revealed by the difference between high and low interference conditions, was equivalent to the effect size in the control group. For the blocked naming task, there was no significant difference between OV and the control group for both responses times and response accuracy. Most notably, OV did not show specific difficulties when she had to name homogeneous set of stimuli. Overall, these results indicate that semantic control processes were well preserved in OV. This is in agreement with the conclusions of previous studies using group comparisons suggesting that semantic control is not impaired in semantic dementia.

- Patient AJ: In contrast to OV, AJ showed a significantly lower proportion of correct responses as compared to the CTRL group in the semantic judgment task. However, there was no significant difference for the high and the medium interference conditions. The only significant difference was found for the lowest interference condition, presumably because the age-matched CTRL group showed a ceiling effect in that condition. Most notably, AJ showed a significantly slower mean response time in the high interference condition as compared to control subjects. The size of semantic interference effect in AJ was also significantly greater than in the CTRL group. In the blocked naming task, response times for the heterogeneous set of stimuli did not differ between AJ and the CTRL group. In the homogeneous condition, the pattern of response times from the cycle 2 to the cycle 4 significantly differed between AJ (i.e. RTs progressively increased) and the CTRL subjects (i.e. RTs remained stable). She also made significantly more errors for homogeneous sets of stimuli, and produced more substitutions. Overall, AJ's performance in lexico-semantic processing tasks greatly depended on the level of semantic interference, suggesting that semantic control deficits can be found in some patients with SD.

- Patient EC: Although the overall proportion of correct responses in EC was not significantly lower than in the CTRL group for the semantic judgment task, the size of the semantic interference effect was larger in EC, due to his poor performance in the high-interference condition. In addition, EC responded faster than healthy elderly subjects in the HI condition but not in lower interference conditions. This suggests that inhibition mechanisms necessary for semantic interference resolution were impaired in EC, leading to fast but incorrect responses. It is important to mention that EC also showed an increased interference effect in the visual judgment task in which we used the same tasks conditions but with visual stimuli (i.e. pairs of geometric forms). Visual judgment deficits were not observed in the AD patients group, OV and AJ. Notably, EC had a history of attentional deficits

when he was recruited. Thus, the poor performance of EC in the high interference condition might be due to general and amodal inhibition deficits, rather than isolated semantic control deficits.

3.2. Experiment 2

The semantic judgement task used in experiment 1 had been adapted for use in an fMRI scanner in experiment 2. The experimental protocol had been piloted at the Cyclotron Research Center of the University of Liège and the ethics committee of the University Hospital had approved this study. In 2013, the Cyclotron Research Center had started the replacement procedures of the SIEMENS MRI 3T Allegra scanner by a new SIEMENS MRI 3T Magnetom Prisma. Unfortunately, the MRI scanner replacement was delayed (April 2015) and the beginning of imaging data collection has consequently to be postponed. To date, 7 patients with AD (out of 16) and 8 healthy elderly subjects (out of 16) could be scanned for this study. The recruitment and the data acquisition are still in progress in collaboration with the Psychology and Neuroscience of Cognition Research Unit of the University of Liège and the Cyclotron Research Center. The fMRI experiment is planned to be finished in the course of 2016, as well as the submission of a manuscript describing its results. In line with previous results (1-3), we anticipate that AD patients will show impaired brain activation in the left inferior frontal gyrus, and possibly in the posterior temporo-parietal junction for the highly interfering task conditions.

3.2. Summary

These results are in agreement with our main hypothesis that semantic control is impaired in AD, and that inhibition deficits at this level may lead to progressive difficulties in processing multiple, consecutively presented semantically-related words. AD patients are likely to produce erroneous responses in this context, and to substitute the correct response by a related lexical or semantic representation. To our knowledge, this is the first experiment showing that AD patients' difficulties in lexico-semantic tasks depend, at least partially, on semantic control deficits. Unlike previous studies of Jefferies et al. (1-2), our results also suggest that semantic control mechanisms are not necessarily preserved in semantic dementia, some patients with SD showing abnormal patterns of performance in highly interfering task conditions. Brain imaging data acquisition, which is still in progress in our laboratory, will help to identify the neural substrates of semantic control deficits in AD.

4. Valorisation/Diffusion (including Publications, Conferences, Seminars, Missions abroad...)

Peters F., Salmon E., Majerus S. (2016). Can the Semantic Interference Between Concepts Modulates the Lexico-Semantic Deficits in Alzheimer's Disease? In preparation.

Van Calster, L., D'Argembeau, A. Salmon, E., Peters, F. Majerus, Steve (2015). Fluctuations of the Attentional Network and the Default Mode Network During the Resting State Reflect Variations in Cognitive States: Evidence from a Novel Resting-state Experience Sampling Method. *Journal of Cognitive Neuroscience,* (Submitted).

Belayachi S., Majerus S., Gendolla G., Salmon E., Peters F., Van der Linden M. (2015). Are the Carrot and the Stick the Two Sides of Same Coin? A Neural Examination of Approach/Avoidance Motivation During Cognitive Performance. *Behavioural Brain Research,* 293, 217-26.

Majerus S., Cowan N., Péters F., Van Calster L., Phillips C., Schrouff J. (2014). Cross-Modal Decoding of Neural Patterns Associated with Working Memory: Evidence for Attention-Based Accounts of Working Memory. *Cerebral Cortex*, 26 (1), 166-179.

Tam A., Orban P., Dansereau C., Belleville S., Benoit S., Dagher A., Joubert S., Monchi O., Peters F., Rosa-Neto P., Rouleau I., Shmuel A., Breitner J.C.S. and Bellec P. (2014). Connectome-Wide Analysis of Differences Between Normal Aging, Mild Cognitive Impairment, and Dementia of the Alzheimer's Type Using Resting-State fMRI Connectivity. *Alzheimer's & Dementia*, 10(4), 47-48.

In February 2014, I was trained in the used of novel neuroimaging data analysis methods during a short mission in Montreal (Canada). These functional connectivity analyses have been developed by Pierre Bellec's team at the Geriatric Institute of the University of Montreal, and are used to investigate patterns of co-variation in patients' brain activity (4). These tools complement those developed in our laboratories which are used for predicting brain networks associated with task-conditions (5).

5. Future prospects for a permanent position in Belgium

The end of this grant co-occurs with an absence of available FNRS permanent research positions or other opportunities as a principal investigator at the University of Liège. To date, no permanent position has been offered to FP elsewhere in Belgium.

6. Miscellaneous

(1) Biegler et al., Cognitive Neuropsychology (2008)
(2) Jefferies et al., Brain (2006)
(3) Peters et al., Human Brain Mapping (2009)
(4) Bellec et al., Neuroimage (2015)
(5) Schrouff et al., Neuroinformatics (2013)