Retirement and Alzheimer's disease

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By drawing on the database from the ICTUS/DSA study (Impact of Cholinergic Treatment Use/Data Sharing Alzheimer), whose objective was to examine the natural history of Alzheimer's disease and the effect of symptomatic treatments involving the use of inhibitors and the socioeconomic impact of the condition, researchers revisited a British study which tended to show a non-negligible link between the age of retirement and the onset of the disease. The results showed that there is an association, but to a lesser degree than previously suggested. The only certainty that emerged from the study was that, in order to untangle the relationship between retirement age and changes in cognitive functioning, including the emergence of a neurodegenerative dementia, there are probably a vast number of variables that need to be taken into account. Article published in PLoS One.

Some twenty years ago, the concept of "cognitive reserve" emerged which held that all activities that we undertook in our lives help us to develop a kind of mental reserve which can enable us to compensate for the cognitive decline associated with normal aging or Alzheimer’s disease. Today, scientific literature abounds with articles that highlight the protective role of different proxy that are supposed to provide the cognitive reserve such as: having a high level of schooling, an active lifestyle, a profession that requires a certain complexity, having pastimes that are culturally enriching, having a well-developed social network...

Nevertheless, the mechanisms that underpin the cognitive reserve remain relatively unknown. There is a commonly-established link between this concept and that of brain plasticity. Put another way, the richer our activities are from a cognitive point of view, the more we develop alternative networks that we can use to counteract the deficiency of networks affected by natural or pathological ageing. But is there a direct correspondence between cognitive reserve and brain reserve? Some dispute this, arguing that the first covers
a much vaster field than the second, in particular, because it calls into action psychological factors (motivation, for example) which make for better use of the available cognitive resources.

**A disputed study**

Whatever the case may be, many studies have established a link between factors contributing to the construction of cognitive reserve on one hand and a decrease in the risk of developing Alzheimer's as well as an increase in the period of time preceding its eventual onset.

As pointed out by Catherine Grotz, a young doctoral student and research fellow at the Belgian Fund for Scientific Research (F.R.S.-FNRS), in the Psychology of Senescence Unit directed at the University of Liege by Professor Stéphane Adam, the professional sphere can be considered to be an environment that lends itself to developing social contacts and the exercise of cognitively stimulating activities, two sources which enrich the cognitive reserve. In an article entitled *Retirement age and the age of onset of Alzheimer's disease: Results from the ICTUS study* (1), published in February 2015 in the journal PLoS One and of which she is the first author, the researcher also points out that several studies have demonstrated that leaving the professional sphere brings about radical changes in an individual's way of life and can affect their cognitive function. However, for the moment only two research articles relating to the impact of retirement on the risk of developing Alzheimer's and the time of its onset have been published.

Published in 2010 in the *International Journal of Geriatric Psychiatry*, the first article (2) to deal with this subject was completed under the direction of Michelle K. Lupton, of King's College London. Catherine Grotz and an international team of researchers wanted to revisit the data from this article especially since the links between retirement and cognition constitute a particularly sensitive subject which may become a political football at a time when attempts are being made to extend the age of retirement under the pretext that this would be good for the health of all the individuals concerned.

Following their work, Lupton and her collaborators reached the conclusion that each extra year of work can delay the onset of Alzheimer's by 0.13 of a year, that is to say, around a month and a half. However, it seemed to Catherine Grotz and her co-authors of the article published in *Plos One* that, while interesting in itself, the article of Lupton and colleague was open to criticism from a methodological point of view. The first point to make is that Lupton's sample (which included 382 individuals) selected from a database containing 938 individuals did not include any women. Not only did the exclusion of women reduce the size of the sample but it also impeded generalization of the results.
A second limitation to be found in Lupton's paper is the fact that it is difficult to determine the parameter upon which the appearance of Alzheimer's is based: the age when the first symptoms manifest themselves (a subjective, self-reported parameter) or a more objective and more reliable parameter: the age at diagnosis.

**Two major biases**

On an even more fundamental level, the study directed by the researcher from King's College London is affected by two biases. The first concerns the selection of the sample. In fact, only individuals diagnosed with Alzheimer's disease are taken into consideration to the exclusion of the normal aged population. In addition, in order to be sure that it is indeed retirement that has an impact on the time of onset of the disease and not the opposite - some people might have stopped working due to previously detected cognitive
problems (reverse causality) - Lupton and her collaborators excluded from their sample all individuals that had been diagnosed with Alzheimer's before their retirement. This is not sufficient to take account of the reverse causality, all the more so because it has already been shown that the \textit{prodromal} phase of the disease can begin up to 10 years before the first diagnosis of dementia is made \cite{3}.

"\textit{Given such a selection strategy, the British researchers created an overestimation of the effect of retirement on Alzheimer's disease}," comments Catherine Grotz. "\textit{In fact, if we apply the two conditions they defined (inclusion of Alzheimer's patients who were diagnosed after beginning their retirement), a worker who left the working environment at 60 years of age, for example, can only have developed the disease after the age of 60, while another who continued his job until the age of 65 or 70 can only develop the disease after this age. In other words, those who leave work at a later age are necessarily those who are most likely to be diagnosed with Alzheimer's at an older age}.

**Lupton revisited**

In the light of these factors, Catherine Grotz and her collaborators set themselves the objective of studying the association between retirement age and age at onset of AD (i.e., onset of first symptoms and diagnosis of AD). They did so by taking into consideration the two biases which could explain the results presented by Lupton in favor of the theory of cognitive reserve.

In order to successfully conclude their work, the researchers focused on the database created from the ICTUS/DSA study (\textit{Impact of Cholinergic Treatment Use/Data Sharing Alzheimer}), whose objective was to examine the natural history of Alzheimer's disease, the effect of symptomatic treatments relying on the use of inhibitors and the socioeconomic impact of the condition. Conducted between 2003 and 2005 in 12 European countries (France, Switzerland, Italy, Spain, Greece, Germany, Belgium, Romania, Great Britain, Holland, Sweden and Denmark), The ICTUS study recruited 1,379 patients with a probable diagnosis of Alzheimer's, 64.7\% of whom were women.
Based on precise exclusion criteria (never having worked, having left the work environment before the age of 50, being still active professionally, having been diagnosed with Alzheimer’s before retirement), the authors of the article published in PLoS One selected 815 individuals from the ICTUS database who were at a mild or moderate state of the disease. Initially, they used a similar measure to that used by Lupton, by distinguishing two elements: the age of diagnosis and the age when symptoms first appeared. The results were as follows: in the first case, each extra year of work delayed the onset of Alzheimer's by 0.31 years; in

Based on these observational data, the causality remains indeterminate: is it really retirement that has an impact on the appearance of Alzheimer’s disease or is it rather cognitive difficulties that cause people to leave their job?

This figure therefore illustrates that, in order to reduce the reverse causality bias (that is to say, to ensure that the subjects were not in the prodromal phase of the disease and had not retired due to cognitive difficulties), only subjects who retired before the age of 65 and who developed dementia at least ten years after taking their retirement were considered (n = 447). This made it possible to reduce the possibility that the subjects had left their jobs due to memory problems.

In order to limit the selection bias, we restricted the analyses to the centre of the point cloud. In order to do this, we selected a sub-sample of 637 retired subjects at or before the age of 65 and who had not developed Alzheimer’s before this age.
the second case the onset of the disease was delayed by 0.30 years. In other words, the trend described by Lupton was not only confirmed but was, in fact, consolidated.

It was now time to check the biases that were attributed to the British study. First, the selection bias. In order to do this, Catherine Grotz and her collaborators restricted the initial sample to 637 retired individuals who were aged 65 or less and who had not developed Alzheimer's before this age. Under these conditions, the previously recorded effect remained significant but was reduced by half: each extra year of work now only delayed the age of onset of the disease by 0.15 years whatever criterion was applied - the age of diagnosis or the age when the first symptoms appeared.

It was still necessary to deal with the reverse causality bias, that is to say, to ensure in as far as it was possible to do so, that the subjects of the study were not in the prodromal phase of the disease and had not therefore retired due to cognitive difficulties. What was the best way to proceed? The best way to proceed was to only retain for the purposes of the study retired individuals aged 65 or less who developed a form of dementia at least 10 years later. "At this point there were 447 individuals left in the sample", explains Catherine Grotz. "It emerged that, among this group, an extra year of professional activity delayed the age of onset of Alzheimer's by 0.06 years on average. This figure was no longer statistically significant; it was in-keeping with the trend".

This result also requires a prudent approach with regard to the conclusions that can be drawn from the links that exist between these two parameters of the age of retirement and the age of onset of Alzheimer's disease. "Only prospective longitudinal studies can truly establish the accuracy of the conclusions", insists the ULg psychologist.

Untangling the web

Other questions merit further exploration. There is a link between retirement and the cognitive function of an elderly person. However, it is important to qualify these results by taking into account the different factors that could play a role in this link.

In particular, it has been observed that the effect of retirement is more marked in men than in women (4). From a social point of view, and in a general sense, work constitutes the central identity of men. Upon retirement, men go "from everything to nothing". This effect is less marked in women who are more apt to become involved in other activities (housework-related tasks and the education of children, for example). "It should be noted that this effect may no longer be present among future generations", says Catherine Grotz.

The type of profession is probably not insignificant either. "Two studies (5) carried out among normal subjects have demonstrated that the negative effect of retirement only continues for white-collar workers, that is to say, intellectual-type professions", indicates Catherine Grotz. This is understandable: Once retired, a manual worker has more leisure time opportunities to take up activities whose cognitive element is more pronounced than during his career as a "blue-collar" worker.

To sum up, we should ask the question as to whether the effect of retirement on cognition is only a brain issue because if a long number of years of work make it possible to stimulate the brain for a longer time and therefore participate in the creation of the cognitive reserve, psychosocial factors (sense of usefulness and self-esteem) also have a role to play (6). An analogy with holidays can be drawn here. When we are working we are cognitively alert: we manage different activities, life is punctuated by work and weekdays. When we plan holidays, we are full of good intentions and we plan to indulge in a full complement of activities. When we arrive in the holiday destination, the plans go out the window, we become cognitively relaxed and after a few days we no longer even know what day of the week it is. If we tested our cognitive performances before and
after the holiday, there would certainly be a difference which would be explained by this cognitive relaxation. The effect of retirement is probably similar to that of holidays. In the retired individual, the brain relaxes and this certainly has an impact on cognition.

"It is becoming more and more evident that psychological and social factors and not biological ones affect the memory", explains Catherine Grotz. "We therefore think that retirement can also influence memory function via these psychosocial factors. Retired individuals are the target of certain negative stereotypes, a form of ageism whose harmful effect on cognition has been demonstrated. For example, the simple fact of activating negative stereotypes linked to age (cognitive decline with ageing and comparison with the performance of younger individuals) has an impact on memory performance in elderly subjects (7). The newly retired individual can sometimes have the impression of being less useful and being a burden to society which could have a negative effect on his memory performance".

Catherine Grotz also points out that a study(8) conducted by Ross Andel (University of South Florida) shows that a lack of intellectual stimulation at work can be compensated by leisure activities characterized by their richness in a cognitive sense and vice-versa.

Another point, among others which needs to be raised is the following: what is the cognitive impact of retirement according to whether it is voluntary or imposed? In short, in order to untangle the web of relations between the age of retirement and the consequent evolution of cognitive faculties, including the appearance of a neuro-degenerative dementia, there is probably a multitude of variables to be taken into account. Examination of the respective influence of some of these will be central to a future scientific contribution by Catherine Grotz.

