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Visuo-spatial working memory and ageing: behavioural, psychophysiological and hemodynamic correlates

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The art of losing isn't hard to master;
so many things seem filled with the intent
to be lost that their loss is no disaster.
Lose something every day. Accept the fluster
of lost door keys, the hour badly spent.
The art of losing isn't hard to master.
Then practice losing farther, losing faster:
places, and names, and where it was you meant
to travel. None of these will bring disaster.

Elizabeth Bishop

Abstract

Working memory is a fundamental function that allows one to perform everyday actions, being involved in academics, professional and social lives. It is negatively influenced by aging. But despite large number of studies, less is know about the visuo-spatial store. In order to better understand this change three studies were carried out, two with healthy participants and one with Parkinson's disease patients. The participants performed a visuo-spatial n back task with low and high cognitive load conditions as well as a control one. In the first one the behavioural data of participants aged from 20 to 80 years was collected in order to better understand the aging process, in particular to see when it starts to become visible and to observe if the cognitive reserve had a positive influence on it. In the second one behavioural, hemodynamic and electrophysiological data was collected from adult and elderly participants, with the same educational level and cognitive reserve. In the last one, behavioural data from a Parkinson's group on medication was collected and they were paired with control participants; the groups had high educational level and cognitive reserve in order to see if these prevent cognitive decline. The results of the first study showed that reaction time started to decrease before accuracy (34 vs 57) and that ageing has a negative effect on both; in reaction time ageing showed an interaction with the 2 back condition. Cognitive reserve due to educational level had positive effects on both and the total cognitive reserve score was a positive factor on accuracy results. In the second study, healthy aging impaired both the selection of response and the working memory processes: inhibition, updating and maintenance. On the other hand, in the elderly group compensation was found in the attention process. Those changes were visible in behavioural, hemodynamic and electrophysiological correlates. In the last one, the patients showed no difference in behavioural results from the control group, showing that total cognitive reserve and cognitive reserve due to work had a positive effect on this. Visuo-spatial working memory is negatively affected by aging, but cognitive reserve and educational level can prevent this effect.

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THEORETHICAL SESSION

EXPERIMENTAL SESSION

CHAPTER ONE

An overview of working memory

1.1 From the memory concept to a working memory model

Memory is an essential cognitive function that allow us to encode, to maintain and to recall information from the past, in order to use it for present or future goals. It is the sum of everything that we have learned before, both about ourselves and about others as well as experiences, skills, facts and habits.

Since this function is involved in our daily lives it has been studied or at least taken into account for a long time. Around 2300 years ago, Aristotle in his "On the Soul" treatise defined memory as a phenomenon whereby things from the past come into the mind in the present. In Ancient Rome, Cicero and Quintilian expanded the knowledge of memory, developing the method of loci, a technique for increasing the quantity of items remembered. This method was then used by Giordano Bruno in the Renaissance period. Moreover, the first word referring to memory was the latin "memoria", meaning "mindful" and "remembering". In the 15th century the current term "memory" with the significance it has nowadays, was used for the first time.

The founding fathers of psychology, William James and Wilhelm Wundt as well as Ernst Meumann in the 18th century, carried out some memory experiments and they created the dissociation between short and long term memories: the former as a temporary store and the second as a permanent one (Atkinson & Shiffrin, 1971). After that, during the Behaviourism period, this theory received little attention until the 1950s, when Donald Broadbent, Donal Hebb and George Miller revived it (Atkinson & Shiffrin, 1971). In particular, the latter showed that short term memory had a certain amount of information that it could store (span), which was the magic number 7±2 (Miller, 1956). Later, Atkinson and Shiffrin (1968) defined a new model of memory, characterized as three different sub-components: a sensory memory, a short-term memory and a long-term one. The sensory memory is the shortest one; it retains information only for 200-500 milliseconds. The trace is in the same format as the information perceived from the environment (by the five senses) and people are usually unaware of the fact that they are using this function. The span is around twelve items: people are not able to report all of them, but they have the perception to have seen such items (Sperling, 1960). Short-term memory is a pivotal store, through it the subject can decide, by control processes, to retain the information or not. The information will decay after 30 seconds (Atkinson & Shiffrin, 1968). Finally, long term memory is a store that contains an unlimited amount of information that had previously arrived from the short term memory for an indefinite period (Atkinson & Shiffrin, 1968).

The term “working memory” was used for the first time by Miller, Galanter and Pribarm (1960) and then re-proposed by Baddeley and Hitch (1974), to refer to a new concept of short term memory, different from the one previous described by Atkinson & Shiffrin (1968). The main difference between the two was that working memory in the second concept is not represented by a unitary store, but is made of three different parts: the phonological loop, visuo-spatial sketchpad and central executive (Baddeley and Hitch, 1974). The phonological loop is formed of two sub-parts: one is the phonological store, which can maintain the trace for a few seconds and the other one is the articulatory rehearsal, which can maintain the information through the repetition of it. It evolved for language learning (Baddeley, 2003). There is some experimental evidence that supports this concept of the phonological loop. A highly robust one is the phonological similarity effect: when the stimuli are similar each other, the probability that the participant could commit errors increases; however this store is not involved when the rate of errors is around 50%, since the participant from this point onwards starts using other strategies (Baddeley, 2003). In addition, the length of the words creates an effect. When the word length increases from one to five syllables, the span declines. This effect disappears when the rehearsal is prevent (Baddeley, 2003). This is due to the trace decay assumption: the last part of the word is more difficult to remember because it is over the store limit (Baddeley, 2003). Finally, there is also an effect concerning irrelevant sound. Irrelevant spoken material has a negative effect on the task performance, independently of similarity between irrelevant spoken material and task stimulus (Baddeley, 2003). What is critical in order to obtain the effect is that the herded items fluctuated. This characteristic of the stimuli generates a conflict and causes a decay in the trace present in the store (Baddeley, 2003).

The visuo-spatial sketchpad holds and manipulates information about visual characteristics and spatial ones; there is evidence about those different subparts, also if they normally interact (Baddely, 2003). The visual cache, responsible for the elaboration of the visual characteristics of the environment, is influenced by the similarity of the stimuli presented (like the phonological loop) (Baddeley et al., 2003). This is true for both letters and shapes as stimuli: when the distractors are similar to the target, they are more difficult to remember (Logie et al., 2000 in Mammarella, 2008). There are also another two effects, one due to ignored images and the other one due to dynamic visual noise (Mammarella, 2008). The first effect was found by Logie in 1986, but was not completely replicated. Dynamic visual noise, consists in showing black and white dots in random positions of the screen; this interferes with the task (Mammarella, 2008). A limitation of this concept is that in one study it was discovered that it interfered with the visuo-passive system, while in another one the authors found that it interfered with imaginative rather than mnemonic tasks (Quinn & McConnell, 1999; McConnell & Quinn, 2000 in Mammarella, 2008). The inner scribe normally elaborated the spatial characteristics of the context and this shows some effects as well (Mammarella, 2008). The suppression effect occurs when a spatial main task is accompanied by another second spatial task (Mammarella, 2008). The types of tasks that generated the interference are: spatial tapping, which consist of touching a series of dots in a specified order (Farmer, Berman & Fletcher, 1986; Salway & Logie,1995; Smyth, Pearson & Pendleton, 1988 in Mammarella, 2008), pointing, that consist of indicating with a finger the position of something (Hale et al., 1996 in Mammarella, 2008), ocular movements (Lawrence, Myerson, Oonk & Abrams, 2001; Baddeley, 1986; Pearson & Sahraie, 2003 in Mammarella, 2008), change of attention (Lawrence, Myerson & Abrams, 2004 in Mammarella, 2008) and arms and legs movements (Baddeley & Lieberman, 1980; Lawrence et al., 2001; Logie & Marchetti, 1991; Quinn & Ralston, 1986 in Mammarella, 2008). Lastly, there is also an effect due to the length of the task (Mammarella, 2008). Loisy in 1997 showed that the longer the distance between the first and the last item the less was remembered (Mammarella, 2008).

The central executive is the most important store; it manages the all the other subcomponents (Baddely, 2003). In the model of Baddeley and Hitch (1974) it was less understood; after that, Norman and Shallice (1986) divided it into two parts: the first one, automatic, related to scripts that the subject used in daily life in a conscious way; and a second one, which is activated when routine control is not sufficient. This function is call the supervisory activation system (Baddeley, 2003).

Finally, a fourth store was added to the model in 2000; it was the episodic buffer, the part that contains different episodes; those episodes are formed by different type of information (Baddeley, 2003) (Figure 1).

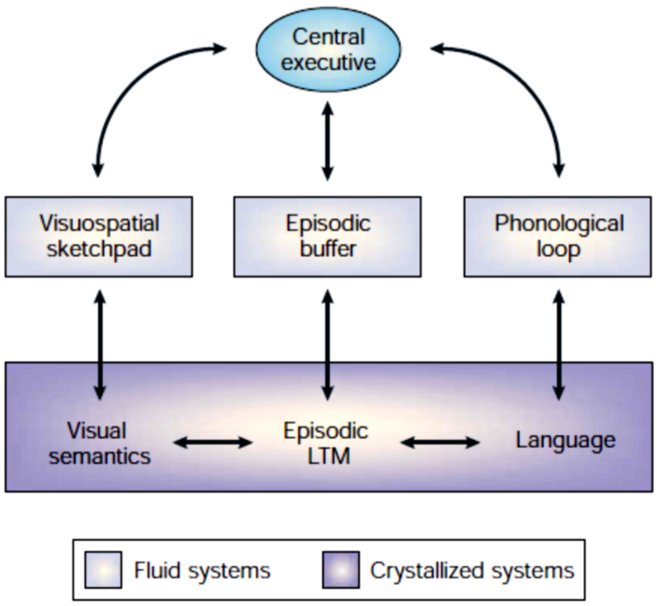


Figure 1 Working memory model, formed by different sub-components (Baddeley, 2003).

1.2 How to investigate working memory

There are several tests that investigate working memory; they are related to information storage and rehearsal on one hand (“simple” measures, like digit span) and simultaneous processing of more items on the other (Turner & Engle, 1989; Case et al., 1982; Daneman & Carpenter, 1980).

In order to measure the span there are numerous tests: Digit Span, Reading-Span task, Operation-span task and Counting-Span task (Mammarella, 2008; Conway et al., 2005). The Digit-span is contained in the WAIS battery, which was created to measure intelligence by Weschler in 1945. It is formed of two parts: in the first one, called Digit-span forward, the participants have to report a sequence of increasing numbers spoken by the examiner. When the participant failed to report the number sequence twice, the task ended and the number of stimuli reported corresponded to the person´s span. The same procedure is used for the Digit-span backward, but the subject has to report the numbers heard from the last to the first one (Weschler, 1945). The Digit span has both a good internal reliability, .70-.90 and a test-retest one, .50-.70 (Conway et al., 2005).

In the Reading-span task (Daneman & Carpenter, 1980) the participants have to read from two to six phrases and for each of them they have to judge and report if it is true or not and, at the same time, they have to learn and to report at the end of the session the last word of the phrase. In the Operation-span task, the instructions are the same, but instead of reading and judging the correctness of sentences, participants have to solve simple mathematical operations and at the end of each trial they have to read out loud the answer (Turner & Engle, 1989). An example of one item: “Is 4/2+3=? (yes or no) DOG.” (Engle, 2002). Finally, in the Counting-span task the participant has to count a series of shapes and to report at the end of the block how many items of a particular shape he or she saw during the task; since it is language-free it is suitable for children, the elderly and non-native speakers (Case et al., 1982). The reliability of reading and operation span is around .70-.80, over minutes (Turley-Ames & Whitfield, 2003), weeks (Friedman & Miyake, 2004; Klein & Fiss, 1999) and more than 3 months (Kleih & Fiss, 1999)

(Conway et al., 2005). Regarding the validity, those span tasks are related to fluid intelligence (Conway et al., 2003). They correlate with each other and with other cognitive functions: comprehension of language, reading and listening, taking notes during class, writing, reasoning, hypothesis formulation, bridge playing and learning of complex tasks (Dameman & Carpenter, 1983; Daneman & Merikle, 1996; King & Just, 1991; Engle, Carullo & Collins, 1991; Kiewra e Benton, 1988; Benton, Kraft, Glover & Plake, 1984; Barouillet, 1996; Kyllonen & Christal, 1990; Dougherty & Hunter, 2003; Clarkson-Smith & Hartley, 1990; Kyllonen & Stephens, 1990 as cited in Coway et al., 2005) and diverge from simple tasks (Conway et al., 2005).

Digit, Reading and Operation span tasks are appropriate to investigate the verbal part of the working memory; for the visuo-spatial one, there are other tests, such as the Corsi block tapping test and Visual Pattern Test as well as the counting span. The Corsi block tapping test consist of remembering a sequence of tapping cubes performed by the experimenter and, like in the Digit-span task, the number of stimuli to remember increases if the subject performs correctly. The task is made up of two parts: in the first one the person has to remember the sequence in the same order as he or she saw it and in the second one the order reported should be inversed (Corsi, 1973). The Visual Pattern Test (Della Sala et al., 1999) consist of remembering a series of grids formed by white and black rectangles; the participants have to show in an empty grid the same pattern that they saw before. This pattern in every item increases in complexity.

Brown-Petterson’s is a well-suited task for measuring working memory, since it correlates with working memory span measures of .59. The task consist of remembering a list of words that are followed by a counting backward task (using this method the participant cannot use strategies for remembering the words); the number of items reported by the subject is the span (Conway, 2005). The same is true for the transformation span, which also correlated with working memory span; additionally, it correlates with reading of .60. In this task, participants have to report a series of items learned before, but in a different order; for example, if the task consists of reporting a series of words, he or she has to report them in alphabetical order (Conway, 2005).

Finally, there are another three tasks, which are more dynamic: running span, keeping-track and n-back (Conway, 2005).

In the first one the subject has to report the last word of a list, without knowing in advance in which position it is going to be, since the number of items presented varies all the time. In this way, continuous updating is required to perform the task (Anderson, 1960; Pollak, Johnson & Knaff, 1959; Waugh, 1960 in Conway, 2005). Similarly, in the keeping-track task, a list of words of different categories that change in length each time is shown. The task consists of reporting the last word of each category (Yntema & Mueser, 1960, 1962 in Conway, 2005). Finally, the n-back task consist of remembering the identity or the position of the stimuli presented n times before. Usually it is formed by a control task, called 0 back and different load conditions; for example in the 1 back one is required to report if the stimulus is the same as the 1 before, in the 2 back if the stimulus is the same as the one 2 stimuli before and so on (Kirchner, 1958; Machworth, 1959). It requires maintenance of the information, updating, information processing, temporal order and inhibition (Kane & Engle, 2002; Suchan, 2008). The running-span correlation are not known yet, while for the Keep-tracking task correlations with Brown-Peterson, span and fluid intelligence were found (Oberauer et al, 2000; Oberauer et al., 2003; Salthouse, 1995; Salthouse, Babcock & Shaw, 1991 in Conway, 2005). Regarding the n-back task, Conway (2005) also reported that if the n-back task is the gold standard of cognitive neuroscience research (Kane & Engle, 2002) it is not clear yet if it is a measure of working memory function, since it correlates with .27 for Digit span and only .14 for the Brown-Peterson task. Moreover, the 2 and the 1 back tasks correlated with .38 for each other. Due to the correlation of different condition of the same task, the correlation between n back and Digit span reported above, seems to be quite high and the authors concluded by saying that n-back seems a more appropriate measure for short-term memory than working memory (Conway et al., 2005). However, other studies report the opposite. The reliability is mixed between the studies, ranging between .02 and .91, being high, around .80 in higher levels (n back 2 and 3), probably due to the fact that the simpler level of the task (n back 1) has a ceiling effect (Friedman et al., 2006; Firedman et al., 2008; Hockey & Geffen, 2004; Kane et al., 2007; Oberauer, 2005; Salthouse, Atkinson & Berish, 2003; Shamosh et al., 2007; Shelton et al., 2009; Van Leeuwen et al., 2007 in Jaeggi et al., 2010). Moreover, the n back task correlates with general fluid intelligence measures: negative correlations are found with reaction times (Gevins & Smith, 2000; Hockey & Geffen, 2004) and positive with accuracies (Daneman & Merikle, 1996; Fry & Hale, 2000; Just & Carpenter, 1992; Kyllonen & Christal, 1990; Miller & Vernon, 1992 in Jaeggi, 2010). Concerning the validity, some studies, like Conway et al. 2005, report a weak correlation between n back and reading or operation span task, between .10 and .24 (Colom et al., 2008; Kane et al., 2007; Oberauer, 2005; Roberts and Gibson, 2002; in Jaeggi et al., 2010). However, two studies, using the same tasks, report a correlation of .46 when they used a unique value formed by all the n back condition (Shelton et al., 2009; Shelton, Metzger & Elliott, 2007 in Jaeggi et al., 2010). The same was true for another study in which the authors collapsed the operation, reading, symmetry and rotation spans in one value; the correlation was .55 (Shamosh et al., 2008 in Jaeggi et al., 2010). Moreover, it could be that span task measurements and n back have some processes in common, but with the correlations, it is not possible to see it (Gray et al., 2003; Kane et al., 2004 in Jaeggi et al. 2010). Kane and Engle (2002) report that working memory was theorized as a system formed by short term memory plus a component related to execution and attention (Baddeley & Hitch, 1974; Baddeley & Logie, 1999; Cowan, 1995; Cowan, 1999 in Kane & Engle, 2002). The correlation between span tasks and tasks that require high cognition response reflect the executive-attentional part of the working memory model. The authors argued that the differences in the working memory tasks are due to the variability among the people in the executive attention (Kane & Engle, 2002). That function is used when people have to maintain a certain amount of information in order to achieve a goal, for example doing a task, when there is other similar information that can interfere with it. The interference is the core of this type of response since if there are no distractors in the environment the process required is just to recall information from the long term memory store (Kane & Engle, 2002). Moreover, maintenance in an active way and preventing distraction are interdependent of each other and they are fundamental for both working memory function and general fluid intelligence (Kane & Engle, 2002). This theory of working memory differs from the traditional one: the quantity of information to recall is important, but not as important as maintaining information in order to realise a goal in a context in which also concurrent information is present (Kane & Engle, 2002). Due to this and to the fact that n back is suitable to manipulate directly the different working memory processes, it is a good tool for investigating experimentally working memory function (Jaeggi et al., 2010). In particular, it was and still is used to test the correlates of working memory: behavioural, electrophysiological and neuroanatomical.

1.3 Behavioural, neuroanatomical and electrophysiological correlates of working memory

From an experimental point of view, working memory, as already mentioned in the previous section, is usually investigated with the n back task, due to its suitability to manipulate different sub processes of that function. Different studies use different stimuli, some of them are related to the phonological loop and some of them are related to the visuo-spatial part of the working memory. In literature, the first function mentioned is the most studied.

Owen in 2005 made a meta-analysis in order to highlight the results from the studies that used the n back paradigm and he divided them in two ways. The first one was about the modality: verbal and none; in the first case, the stimuli were letters or words and in the second one, the stimuli were shapes, faces and pictures. The second one was regarding the task: identity and location.

1.3.1 Behavioural correlates of working memory

Most of the previous studies had the main goal of investigating neural or psychophysiological correlates of working memory, so in all of them the reaction times and the accuracies were recorded together with the techniques, such as PET, fMRI, fNIRS or EEG.

In the studies that focused on the identity of the material the participants had to respond when the stimulus was the same as that of n times before (normally it ranged from 1 to 3). Most of them had a control condition as well, called 0 back task. The majority of the studies only report the pattern of the data, few of them reported the accuracies and the reaction times in different conditions.

The type of stimuli can be divided in verbal and not verbal. The verbal tasks consists in remembering letters or words; the not verbal task consists in remembering the identity of the stimulus. A total of twenty studies were found, thirteen verbal and seven not. More details are reported in the table 1.

Authors and year of publication	**Type of stimulus**	**Conditions used**	**Accuracy results**	**Reaction times results**
		Studies with verbal stimulus		
Braver et al., 1997	letters	0, 1, 2 and 3		484±24 ms, 539±35 ms, 628±45 ms and 701±45 ms
Ragland et al., 2002	letters	0,1 and 2 back	Accuracy deceases as n increase	Reaction times increase as n increases
Raemae et al., 2000	letters	1 and 3 back	Accuracy decreases in 2 back	Reaction times increase as n increases
Brouwer et al., 2012	letters	0,1 and 2 back	96%, 93% and 89%	533 ms, 595 ms and 526.6±4.3 ms

West, Bowry & Krompinger, 2006	letters	1 and 3 back	Accuracy deceases as n increase	Reaction times increase as n increases
Tanaka et al., 2012	letters	2 back	Accuracy decreases in 2 back	
Spronk & Jonkman, 2012	letters	0 and 1 back	Accuracy decreases in 2 back	Reaction times increase as n increases
Coffey, Brower & van Erp, 2012	letters	0,1 and 2 back	No differences due to condition	No differences due to condition
Pesonen, Haemaelaeinen & Krause, 2007	letters	0, 1, 2 and 3 back	Accuracy deceases as n increase	Reaction times increase as n increases
Braver & Cohen, 2001	words	0, 1, 2 and 3 back	Accuracy deceases as n increase	Reaction times increase as n increases
Kim et al., 2002	words	2 back	97.4±5%	
Kim et al., 2003	words	0 and 2 back	99.3±1% and 99.8±0.5%	
Chen & Mitra, 2009	words	0,1 and 2 back	Accuracy deceases as n increase	Reaction times increase as n increases
Leon-Dominguez, Martin-Rodriguez & Leon-Carrion, 2015	words	0,1 and 2 back	Accuracy decreases in 2 back	Reaction times increase as n increases

Chen, Mitra & Schlaghecken, 2008	words	0, 1 and 2 back	Accuracy deceases as n increase	Reaction times increase as n increase
Studies with not verbal stimulus				
Braver & Cohen, 2001	faces	0,1, 2 and 3 back	Accuracy deceases as n increase	
Dade et al., 2001	faces	0 and 2 back	90% in 2 back	
Druzgal & D'esposito, 2001	faces	0, 1 and 2 back	99.1±0.1%, 89±0.3% and 70±1.1%	505±3.9 ms, 698 ms and 585± 6.4 ms
Callicott et al., 1999	numbers	0, 1, 2 and 3 back	99±3%, 95±6%, 88±15% and 81±23%	
Kim, 2002	pictures	2 back	99.3±1%	
Alain et al., 2009	sounds	1 and 2 back	Accuracy decreases in 2 back	Reaction times increase as n increase
Raemae et al., 2000	sounds	1 and 3 back	errors: 2.9±0.8% and 19.4±3.9%	1080±62 and 840±49

Table 1 Authors, years of publication, type of stimulus and results of previous studies

Regarding the literature about visuo-spatial tasks, the task usually consisted in remembering the position of the shapes used as stimulus.

The majority of the studies have experimental conditions that ranged from zero to two back (Carlson et al., 1998; Chen & Mitra, 2009; Chen, Mitra & Schlaghecken, 2008). Watter, Geffen and Geffen (2001) used all of these conditions and implemented the 3 back as well. Nystrom et al. (2000) and Valadao, Anderson & Danckert (2015) compared the control condition and the 2 back task. Moreover, another two studies compared the 1 back with the 2 (Luu et al., 2014) and the 3 condition (Raemae et al., 2000), respectively.

Regarding the results reported, most of the studies just report the tendency instead of the values. Three papers reported that accuracies decrease between 2 and the control condition (Nystrom et al., 2000; Luu et al, 2014) while Valadao, Anderson & Danckert (2015) reported that the stimulus was better expected when n increased. Chen & Mitra (2009) and Chen, Mitra & Schlaghecken (2008), reported the same pattern: they had also the 1 back condition. With the same experimental design, Carlson et al. (1998) found no differences in the accuracies. Only two works reported the values. The first one (Raemae et al., 2000) compared the control condition and 2 back and found the following errors rates: 2.5±0.6% and 12.7±3.7%. The second one (Watter, Geffen and Geffen, 2001) compared conditions ranging between 0 and 3 back and the accuracies were: 95.9±1%, 90.7±2.9%, 87.6±3.5% and 77±3.4%.

The same was true for the reaction times. Most of the papers report only the pattern of the data collected. The reaction times increased between 0 and 2 back (Luu et al., 2014; Carlson et al., 1998; Nystrom et al., 2000; Chen, Mitra & Schlaghecken, 2008; Chen & Mitra, 2009). Finally, two studies reported the values. The first one (Raemae et al., 2000) compared only high and low conditions and found these values, respectively: 1009±65 ms and 792±56 ms. The second one (Watter, Geffen and Geffen, 2001) had conditions ranging between 0 and 3 back and the following are the reaction time results: 406±27 ms, 475±32 ms, 554±47 ms and 621±57 ms.

In conclusion, independently from the type of task used, when the load in the working memory increases there is a clear effect on the behavioural data. This effect shows a clear accuracy reduction and reaction times increment due to the number of items before taking into account.

1.3.2 Neuroanatomical correlates of working memory

The neuroanatomical correlates of working memory have been widely studied. Different techniques are used but the most applied one is fMRI which measures the change in the blood oxygenate level in response to a task; this technique gives really good spatial information (Cui et al.,2011). Few studies use PET, probably due to the limit of the technique itself (the signal that this device measures is the same as fMRI, but this technique is invasive) and other used fNIRS, which works like fMRI (Cui et al., 2011); in this case the reason why there are less studies is the recent introduction of this device.

Three meta-analyses give an idea of what was found and, especially in this topic, it is useful since studies used a varied range of stimuli, inter stimulus interval and timing of the presentation of the stimuli.

The first one, made by D'Esposito and colleagues in 1998 had the aim of investigating the different neural correlates between spatial and non spatial working memory. In particular, they studied the neuroanatomical correlates of the "what" and "where" ways in the prefrontal cortex: the first one is related to the recognition of the stimuli and the second is related to spatial information (D'Esposito et al., 1998). These anatomical distinctions came from monkey studies, in which authors showed that the parietal cortex (related to visual information) is anatomically linked to the dorsal region of the lateral prefrontal cortex, while the temporal one (that is related to the identity information process) projects ventrally in the same region (Barbas, 1999; Cavada & Goldman-Rakic, 1989; Petrides & Pandya, 1984 in D'Esposito et al., 1998). 24 studies that used fMRI and PET techniques were selected, with 40 different paradigms used. Among these, only five studies performed a within group design: both spatial and non spatial stimuli were used; the other studies used only spatial or verbal stimulus (D'Esposito et al., 1998). When all the data from these studies is plotted together, there is no evidence for a dissociation between ventral and dorsal distribution of the anatomical correlate due to the stimuli types (D'Esposito et al., 1998). However, the data showed different activations between the stimuli types: the visual tasks activate more the right hemisphere of the lateral prefrontal cortex while the identity/verbal activate more the left one. This result is not absolute: both verbal and visual activate the right hemisphere (Broadmann area 46) and also the supplementary motor area (6 medial), lateral premotor cortex (6 lateral) and the posterior part of the cortex (areas 7, 19 and 40) (D'Esposito et al., 1998). The supplementary motor area is involved in the beginning of a voluntary movement, the lateral premotor cortex is related with saccade movements and the posterior one to the task in general (this result is different from previous studies, in which this activation only got reported due to the spatial tasks) (D'Esposito et al., 1998). Finally, another effect was the load one: at the increase of n, the activation in the region mentioned before also increases (D'Esposito et al., 1998). An explanation for such a difference is that the ventral part of the brain is involved in the immediate recognition of the stimuli and requires active comparison with the information stored, while the dorsal part of the lateral prefrontal cortex is involved in manipulation of the stimuli and the monitoring process (D'Esposito et al., 1998).

Smith and Jonides (1999) made a review regarding the neuroanatomical correlates of the executive process and the working memory stores. They selected previous studies in which PET or fMRI were used and an inclusion criterion was that in the studies were present both a control and an experimental condition (Smith & Jonides, 1999). They took into account Baddeley's model of the working memory, so they analysed the studies coherently with Baddeley's subdivision of the working memory.

Relative to the verbal store, they took into consideration studies that used letters as stimuli; activation was found in the parietal left cortex (Bradman 40 area), frontal part (44), left supplementary motor and motor areas (6) and dorsolateral prefrontal cortex (D'Esposito et al., 1998). The areas found active were the Broca's areas and the others (the frontal ones) are related to the preparation of speech and the rehearsals area in the n back task (Smith & Jonides, 1999).

The spatial tasks activate the prefrontal cortex (both in human and monkeys). Moreover, a dissociation between object and spatial stimuli was found: the first one activated the right dorsolateral prefrontal cortex, while the other activated the right premotor one; a ventral/dorsal dissociation between them (see above for a detailed explanation) was found in the parietal region as well (Smith & Jonides, 1999). Furthermore, like the results in the verbal store, rehearsal activates the right premotor cortex (Smith & Jonides, 1999).

In addition, the central executive was take into account. The inhibition of irrelevant stimuli or information is related to the anterior cingulate cortex, the attention and inhibition in the early stage of the perception activates the frontal one, the dual tasks activate the frontal part, the dorsolateral prefrontal and the anterior cingulate ones (Smith & Jonides, 1999).

Finally, Owen and collaborators in 2005, with the meta-analysis technique, summarized the results found with the n back paradigm relative to the neuroanatomical parts involved during that task. The studies selected totalled 24, all of them used fMRI techniques and in total, there were 668 foci activated (Owen et al, 2005).

Working memory activates the bilateral and the medial parietal areas as well as the precuneus and inferior parietal lobule (Broadmann areas 7 and 40), bilateral premotor cortex (6, 8), dorsal and medial pre motor cortex as well as the supplementary motor area (6, 32), rostral prefrontal areas and frontal pole too (10), dorsolateral prefrontal cortex both left and right (9, 46) and the mid-ventrolateral frontal part (45, 47) (Owen et al., 2005).

The areas activated by verbal and non-verbal tasks are similar to each other, except for the fact that the verbal ones activate more the left part of the brain; localization tasks, on the other hand, activate more the right hemisphere (dorsolateral prefrontal and medial posterior parietal cortex) (Owen et al., 2005). Moreover, the identity/verbal tasks activate the ventrolateral prefrontal cortex in the left part, medial and bilateral premotor cortex, medial posterior parietal cortex in both the right and left hemisphere and thalamus; while non-verbal tasks activate the frontal pole and the dorsal cingulate regions (Owen et al., 2005). Finally, the comparison between identity and location tasks showed that the first one is related to enhanced activity in the right dorsolateral prefrontal cortex, lateral premotor and right medial posterior parietal cortex while identity activated the dorsal cingulate and medial premotor cortex (Owen et al., 2005).

Interestingly, Owen et al. (2005) reported in detail the function of each part of the cortex activated. The dorsolateral prefrontal cortex is involved in the organization of the information to remember (for example using chunking) while the ventrolateral responded to the task in an explicit way; different tasks involved the activation of different parts (Owen et al., 2005). The rostral prefrontal cortex (called the frontal pole as well) is involved when a task requires more than one process; the premotor one is related to the maintenance of visuo-spatial attention. Furthermore, the parietal cortex, is activated in spatial rehearsal processes in the right portion of it while the left part is related to the load of the stimulus (both load and delay) (Owen et al., 2005). Moreover, the dorsal part is independent of the type of the task and the ventral is related to language tasks (like encoding-recoding processes) (Owen et al., 2005).

One study also attempted to compare the difference in activation between spatial and verbal tasks. Hautzel et al. (2009) used the fMRI technique with an n back task, having two conditions: a control one and a 2 back one. The stimuli were letters and shapes without any specific meaning. They found that also the cerebellum responds to the increase of load in the task, but there were no differences between the two types of stimuli (Hautzel et al., 2009).

Finally, Takeuchi and colleagues (2012) used fMRI with an n back task in which participants had to remember numbers in 4 conditions: control, 2, 3 and 4 back. The effect of memory load (comparison between 2 and 0 back) gives the following results: the bilateral dorsolateral prefrontal cortex, left ventrolateral prefrontal cortex and supplementary motor area were active, as well as the inferior and superior parietal lobule in the left hemisphere and the bilateral caudate. This activation is similar to the results of Owen et al., 2005 reported above (Takeuchi et al., 2012). The task speed effect, calculated subtracting higher versus lower speed in both 0 and 2 back conditions, were found in the following areas: the bilateral occipital lobe, left pre and post central gyri, right fusiform gyrus and right thalamus

(Takeuchi et al., 2012). An interaction between reaction time and the right dorsolateral prefrontal cortex were found, while no correlation between brain activation and accuracy was present (Takeuchi et al., 2012). Moreover, the right dorsolateral prefrontal cortex showed a functional connection with the parietal lobe, within the frontal-parietal network (Takeuchi et al., 2012). Additionaly, the dorsolateral prefrontal cortex was correlated with a high amount of grey matter that can explain the speed of the reaction time; no correlation was found regarding white matter (Takeuchi et al., 2012).

Other studies, especially in the last years, used fNIRS in order to investigate working memory. Due to its correlation with fMRI, it is a suitable technique especially because it has some advantages: an ecological setting, it costs less, it does not produce noise during the task and it tolerates movement artefacts well (Masataka, Perlovsky & Hiraki, 2015). Due to these characteristics, fNIRS is an ideal tool to study prefrontal cortex activity (Masataka, Perlovsky & Hiraki, 2015). Some laboratories study the correlation between fMRI and fNIRS results, in order to see if the second one is a suitable technique for obtaining the same results; since the final scope is to use it in a clinical setting, it is necessary to make sure that the data is sensitive and precise enough (Masataka, Perlovsky & Hiraki, 2015). All of them found that fNIRS is sensitive to the change in memory load and to the different states: the comparison was made between the resting state and various load conditions (Herff et al., 2014; Fishburn et al. 2004 in Masataka, Perlovsky & Hiraki, 2015).

Leon-Dominguez, Martin-Rodriguez & Leon-Carrion in 2015 used fNIRS prefrontal montage with 16 channels in order to detect if there were some differences between the load conditions 0, 1 and 2 in an n back task, with the names of days as stimuli. They found that in the channels that cover the left prefrontal cortex the oxygenated haemoglobin increased as the load memory also increased, particularly in the dorsolateral prefrontal cortex and the opercula (Leon-Dominguez, Martin-Rodriguez & Leon-Carrion, 2015).

Herff and colleagues in the 2014 used a similar montage of the fNIRS, with 8 channels, and a verbal (letters) n back task, containing three workload levels and one control condition. An activation of the oxygenate haemoglobin in all the channels was found due to the increment of the working memory load, especially in the 3 back condition, while a clear decrement pattern was seen in the deoxygenated haemoglobin between conditions (Herff et al., 2014).

Additionally, Molteni and collaborators (2009), with an 18 prefrontal montage tested how verbal working memory influenced the hemodynamic response due to different load conditions: control, 1, 2 and 3 back; furthermore, they also analyzed the general pattern of activation during the task. The response of the oxygenate haemoglobin increased, especially in the first part of the task, then remained stable and continued to increase again near the end; the area that continued to respond selectively to the load during all the task was the dorsolateral prefrontal cortex (this could be interpreted as a tonic response) (Molteni, 2009). Regarding the conditions, the highest response was found for the 3 back condition. A similar pattern was found for the deoxygenate haemoglobin. No effect of channels were found, all the prefrontal cortex responded in the same manner, while surprisingly the right prefrontal cortex and the right prefrontal pole had a higher response than the left ones, especially in the second part of the task (Molteni, 2009).

Finally, other studies used a visuo-spatial paradigm in order to find the neuroanatomical correlates of this sub function. Most of them used fMRI, while one used fNIRS.

Van Evijk et al. (2015) used fMRI with a visuo-spatial task in which participants had to remember the position and temporal order of yellow dots that could appear in 16 positions of the screen, delimitated by a grid. There was a control condition and two experimental tasks: one with low and one with high memory load. The active clusters related to the task in general were the middle frontal gyrus, precentral gyrus, superior parietal cortex, insula, thalamus, occipital cortex and cerebellum; all of them were activated bilaterally (Van Evijk et al., 2015). Relative to the memory load, the regions that selectively responded to it were the lateral frontal pole, paracingulate gyrus, inferior, middle and superior frontal gyri and occipital and parietal posterior regions (Van Evijk et al., 2015). The activation due to this task provides different results than the verbal tasks; the more widespread activation (occipital, subcortical and cerebellar) could indicate that this task involved a different network response (Kane et al., 2007; Redick & Lindsey, 2013 in Van Evijk et al., 2015).

Dores and collaborators in 2015 used the same techniques and a similar task (the screen was divided by a grid into nine parts and selectively one of them was coloured black) with two conditions: control and 2 back. The activated areas were: superior prefrontal sulcus (Broadmann area 6), dorsolateral prefrontal cortex (6, 46), bilateral ventrolateral prefrontal cortex (47), inferior frontal gyrus (44, 45), premotor cortex (6), inferior parietal lobe (7, 19, 39), intraparietal sulcus (7) and precentral gyrus in the primary motor cortex (4); visual areas were active as well (17,18) (Dores et al., 2015). The dorsolateral prefrontal cortex is related to the manipulation of the stimuli, while the ventrolateral had a role in the maintenance (Dores et al., 2015). The activation of motor and premotor areas is related to the response required during the task (Dores et al., 2015). The right inferior parietal cortex seems to be the store of the visuo-spatial information of Baddeley's Model (Dores et al., 2015).

Finally, Nakahachi et al. (2010) used fNIRS frontal montage with 52 channels, investigating the correlates of an advanced Trial Making Test: the task consisted of pressing 25 numbers placed randomly on the screen in a numerical order. In one condition, the number remained in the same position throughout the task, while in another one they changed randomly every time the participant selected a number (Nakahachi et al., 2010). Three channels responded to the second condition (which was created just to see the effect of the motor response), while 19 responded to the working memory task; in these 19 channels the 3 that also responded during the other condition were active (Nakahachi et al., 2010). They were placed in the bilateral dorsolateral and ventrolateral prefrontal cortex; this part of the brain is associated with movements and associative sensorimotor learning (Nakahachi et al., 2010). Moreover, both the dorsolateral prefrontal cortex and the ventrolateral prefrontal one are associated with the central executive store of Baddeley's model (Baddeley, 2003); in this study it seems that it shows a stronger response than the visuo-spatial sketchpad store (Nakahachi et al., 2010).

1.3.3 Electrophysiological correlates of working memory

The evoked potential components, collected with EEG, reflect the amount of electrical activity activation due to a stimulus, that refers to a particular condition and that is related to a particular function (Luck, 2005). The information that this type of technique can provide is of three types: the latency, the amplitude and the source. The latency reflects the exact timing in which an event happened (such as a response to a stimuli or the perception) and the amplitude is related to the amount of what we are studying. Finally, the source analysis is related to the cerebral zone that is activated; this is possible only with a certain number of electrodes, the minimum amount being 64 (Michel et al., 2004; Luck, 2005).

Several studies used this tool in order to highlight the of timing working memory function, by analyzing the evoked component registered during n back tasks. Each component could be referred to a particular sub process of the working memory.

The first evoked component in the electroencephalogram due to a working memory task appears around 200 milliseconds after the onset of the stimulus (Halgren et al., 1994; Rainer, Assad & Miller, 1998; Foxe et al., 2005; Luck & Hillyard, 1994; Bar, 2003; Bar et al., 2006; Perianez et al., 2004 in Lenartowics, Escobedo-Quiroz & Cohen, 2010). The localization of this component, called P2, is anterior (Astle et al., 2008; Astle et al., 2008 in Lenartowics, Escobedo-Quiroz & Cohen, 2010). The process that seems to be involved is the general registration of the information seen or heard, in detail it seems to be involved in updating and encoding processes (Lenartowics, Escobedo-Quiroz & Cohen, 2010). In some other studies, no components are find before the P3 one (Wylie et al., 2003; Wylie et al., 2009 in Lenartowics, Escobedo-Quiroz & Cohen, 2010).

Chen and Mitra (2009) used two versions of an n back task: in one of them the participants had to take into account letters, while in the other it was the position of a “$” symbol, with the same length as the words. The conditions were 0, 1 and 2 back. Relative to the P2a, the effect was significant both in central and non central electrodes and the amplitude increased as the load became higher in the middle anterior part; this effect was found only for verbal tasks (Chen & Mitra, 2009).

Alain and collaborators, in the same year, measured change in 64 channels EEG during a task with two memory loads (1 and 2 back), in which there were two conditions: in one they had to give attention to the type of stimulus ("what") and in the other to the location of the stimulus ("where"). The P2 were maximum in the midline frontal-central part, with an inverted response in the parietal-occipital sites (Alain et al., 2009). The sources were located in the superior temporal gyrus.

The P3 is the most studied component. It appears just after 300 milliseconds from the onset of the stimuli in the central electrodes. Relative to the memory task it was studied for the first time in 1984 by Karis et al. and they said that it was associated with the recall process (Polich, 2007). It is related to the target and when it appears, it produces a bigger response; moreover, probability also induces the same growth: less probability is relate to higher amplitude (Polich, 2007). The latency is related to the timing of the evaluation of the stimulus: the correlation between them is positive (Polich, 2007). The P3 is usually divide into two different sub-components, P3a and P3b. The first one is normally found in the central electrode (Cz), while the other is normally in the parietal one (Pz); the latency is shorter in the P3a than P3b and the second one only correlates with the reaction time (Polich, 2007). The P3a, or the novelty P3, is related to the top down attention given to the stimulus; it is involved in the go no-go task, in which the participant has to monitor continually the incoming stimulus (Polich, 2007). The P3b, on the other hand, is related to updating and storing the information (Polich, 2007). They are part of a frontal-temporal-parietal network (Knight, 1990; Polich, 2003; Soltani & Knight, 2000 in Polich, 2007) and the generators are found in those brain areas (Ebmeieret al., 1995; Kirino et al., 2000 in Polich, 2007).

Chen and Mitra (2009) with spatial and verbal tasks (more details are reported above) found an effect of the task in the P3 amplitude: it becomes bigger as the load increases in the posterior part of the brain. Relative to the latency, the stimulus x n back x task was significant: in the spatial task the difference in the latencies was higher in the 1 back condition between target and non target, while in the verbal task the amplitude increased going from the 0 to 2 back condition; the target effect was present only in the verbal task (Chen & Mitra, 2009). Moreover, the P3 showed no hemispheric effect (Chen & Mitra, 2009).

Brouwer et al. (2012) used an n back paradigm with three conditions (control, 1 and 2 back) with letters in order to understand the timing of the working memory. At Pz, the P3 amplitude is attenuated by memory load, but while in the 2 back it is smaller, the 1 back is not in between (Brouwer et al., 2012).

West, Browry and Krompinger (2006) used a task with n back 1 and 3 plus a prospective one. The stimuli were letters and in the prospective condition, the participant had to press one response button when the word was written with a predefined colour (West, Browry and Krompinger, 2006). The P3 was elicited by the target at Pz and the amplitude was smaller in the high load condition (West, Browry and Krompinger, 2006). The P3 amplitude reflects the working memory capacity (Kok, 1997 in West, Browry and Krompinger, 2006). Also Wintink, Segalowitz and Cudomore (2001) used the same n back paradigm (except for the 0 condition) and found the same pattern at Pz; in Cz, instead, there was no change in P3 due to the different load condition and at Fz the P3 increases with n (Wintink, Segalowitz and Cudomore, 2001). Moreover, at Pz, there is a decrease in the P3 after the first blocks and the amplitude of this component is at its' highest in this channel and at its' lowest at Fz (Wintink, Segalowitz and Cudomore, 2001). These results support the hypothesis that there is an initial strong response from the frontal part, that afterwards decreases and the response then becomes more related to the parietal one (Wintink, Segalowitz and Cudomore, 2001). The same result was found by Watter, Geffen and Geffen (2001) in a task in which participants had to remember the position of the stimulus in the control condition and in the 1, 2 and 3 back tasks. Moreover, the latency was earlier in the control condition than in the n back ones, without any difference between them (Watter, Geffen and Geffen, 2001). The constant latency between the n back conditions is because participants use the same response in each stimulus shown (Watter, Geffen and Geffen, 2001). The decrease in amplitude due to the load is consistent with previous findings, both with the same or other paradigms (Gevins et al., 1996; McEvoy et al., 1998; Strayer &

Kramer, 1990; Kramer et al., 1991 in Watter, Geffen and Geffen, 2001) and it represents the reallocation of attention (Watter, Geffen and Geffen, 2001). In another visuo-spatial n back task (Bomba & Singhal, 2010) the P3 was found maximally at Pz and it decreases during the increasing loading in working memory. Additionally, the latency showed an effect: it became slower as the load increased (Watter, Geffen and Geffen, 2001).

The N3 component is a negative component usually found at the frontal or frontal-polar site (Folstein et al., 2008). It is related to the process of response monitoring as well as to the maintenance and it is generated in the anterior cingulate cortex (Niuewenhuis et al. 2003, Yeung, Botvinick & Cohen 2004 in Folstein et al. 2008).

West, Bowry and Krompinger (2006) in an n back combined with a prospective task showed that N3 was elicited by the target and this seems to be related to a phasic state in the occipital-parietal regions (West, Bowry and Krompinger, 2006).

1.4 Ageing and working memory

Studying the process of ageing has always been of significant importance because of its' natural aspect and, consequently, we as human beings are destined to experience it. Better understanding this process allows us to improve our quality of life and by knowing the effects of healthy ageing we can better intervene when pathologies are also involved during this process. Nowadays, given the unprecedented large number of the global population, it has become of vital importance to study this phenomenon because of the large number of people that are subject to this process in the present and are predicted to be in the future. The global population aged 60 and over will more than triple by 2050 numbering 2 billion; a process that has increased from the year 2000 when the estimation was of 600 million (World Health Organization).

Ageing is related to changes in cognitive functions, but while some of them decline, others remain stable. It is well known that functions like processing speed, working memory and encoding of new episodes or facts decline when age increases (Hedden & Gabrieli, 2005). On the other hand, short term memory, knowledge about facts and ourselves as well as emotional processing remains stable during the life-span (Hedden & Gabrieli, 2005). One of the largest studies conducted in this field, the Seattle Longitudinal study, attempted to highlight the changes that occur during ageing and showed that verbal and numerical abilities remain stable, while inductive reasoning, spatial orientation, perceptual speed and verbal ability decline in time. The decline for all functions occur after 55 years of age, except the speed reaction, which starts to decline at an earlier stage (Hedden & Gabrieli, 2005).

One of the goals of the research in this field is to highlight the correlates of the ageing processes and this is possible by techniques such as fMRI, EEG, PET and recently fNIRS. Relative to the anatomical change, it is not uniform in the brain; while the anatomy of some regions remain stable during the life-span, others show changes. Lateral prefrontal cortex as well as the hippocampus show a linear decline in their volume during the life span, but only at around 55 years of age, while the primary visual cortex shows a smaller but stable decline during life span (Hedden & Gabrieli, 2005).

In this work behavioural, neuroanatomical and electrophysiological aging correlates of working memory are shown.

1.4.1 Behavioural correlates of ageing in working memory

All of the studies that use n back as a paradigm in order to investigate the differences due to age have used an identity task. Only one carried out a visuo-spatial n back task but it was a modified version of this task. Van Gerven (2008), Voelcher-Rehage, Stronger & Alberts (2006) and Vaughan et al. (2008) carried out studies in which only behavioural correlates of ageing were taken into account, while in all the other papers found, the aim was to understand the neuroanatomical or psychophysiological correlates as well.

Among the identity studies, six used letters as stimuli (Wild-Wall, Falkenstein & Gajewski, 2011; Daffner et al., 2011; Gajewski & Falkenstein, 2014; Missioner et al., 2004; Vemeij et al., 2012; Voelcher-Rehage, Stronger & Alberts, 2006) and the others used numbers (Mattay et al., 2006; Nyberg et al., 2009; Van Gerven, 2008; Vaughan et al., 2008).

Two studies used control condition and 2 back (Wild-Wall, Falkenstein & Gajewski, 2011; Gajewski & Falkenstein, 2014) and one the same conditions plus one with a memory load between them (1 back) (Daffner et al., 2011). Moreover, in another two papers the 3 back condition was also used (Mattay et al., 2006; Nyberg et al., 2009). Finally, another two works took only 1 and 2 back into consideration, without any control task (Missioner et al., 2004; Van Gerven, 2008); and another one the same conditions plus 3 and 4 back (Vaughan et al., 2008).

Regarding the results, most of the authors report only the pattern of the results found, while a small amount of studies also report the data in the papers.

Three works found a general reduction in accuracy in older participants, independent of the working memory load (Vaughan et al, 2008; Van Gerven, 2008; Daffner et al., 2011). Another one (Nyberg et al., 2009) found that also in the low working memory load (1 back) the elderly participants showed less errors; this was true when they were compared both to high and low load younger performers. In the 1 back condition the results were: 34.73±0.1 in the correct yes and 51.55±3.33 in the correct no for the high younger performers and 33.09±2.21 and 52.09±1.45 in the low performance participants, while the elderly participants showed 29.82±3.87 and 47.55±8.47. In the 2 back condition the results were: 33.45±2.62 and 52.18±4.09 in the high performing subjects and 31.27±3.20 and 51.73±2.28 in the low performing ones, while the results in the older group were: 26.36±3.8 and 47.09±8.24 (Nyberg et al., 2009). Finally, the results in the highest load condition (3 back) were 28.82±4.64 and 51.36±4.95 in the high performing participants and 24.36±1.86 and 50.55±3.70 in the low ones, while elderly performance was 21.29±3.62 and 45.83±9.46 (Nyberg et al., 2009).

In Vermeij and collaborators work (2012) the accuracy decreased because of age and the increase of n taken together. The same pattern was found by Voelcher-Rehage, Stronger and Alberts (2006): the effect of ageing was detectable only in 1 and 2 back, while no differences were found in control condition. In addition, Mattay and colleagues (2006) found an ageing effect in 2 and 3 back only (and not in lower load tasks). The results of Gajewski and Falkenstein (2012) are in the same direction (no differences in control task was detectable, but only in the 2 back one).

Finally, Wild-Wall, Falkenstein and Gajewski (2011) used only 2 back in their work and found a general pattern in which accuracies were higher in younger (94.2±0.7%) than elderly subjects (88±0.8%).

Regarding the reaction time, most of the studies just reported the pattern of the results, while only a few of them also reported the data found.

Most of the studies reported a general reduction in the speed of the response due to age, which was independent from the load in the working memory (Mattay et al., 2006; Missioner et al., 2004; Vaughan et al, 2008; Van Gerven, 2008). The same was found in the Gajewski and Falkestein paper (2014): the older participant was slower both in 0 (467±95 vs 404±37.6 milliseconds) and 2 back tasks (661±16.5 vs 526±15.2 milliseconds). Wild-Wall, Falkenstein and Gajewski (2011), that used only two back condition, found the same results: 494±85.5 milliseconds was the reaction time of the elderly, while 416±76.9 was the result of the younger subjects. Daffner and collaborators in 2011 found that during a single task there were no differences in the task performance due to age, but when the task was a dual, the accuracies decreased. Generally the reaction times of 0 back are similar in the different age groups, while in the 2 back the elderly were slower compared to both high and low younger performers (597±28 vs 499±25 milliseconds) (Daffner et al., 2011).

Only one study, Vermeji et al. (2012) did not find any differences between groups due to age.

As already mentioned above, in only one study was a visuo-spatial working memory paradigm applied; the task used was a modification of the classical n back. The aim was to investigate the difference due to age to the lures stimulus: the one that matched one stimuli before, but that was not a target since the task was a 2 back (Schmiedek, Li & Lindenberger, 2009). The stimulus used was a circle that could appear every time in eight out of nine parts of a 3x3 grid that divided the screen (the stimulus never appeared in the centre) (Schmiedek, Li & Lindenberger, 2009). A significant effect was found for age and the difficulty of the task. The same pattern was discovered in the reaction time.

1.4.2 Neuroanatomical correlates of ageing in working memory

Few studies have investigated the changes in working memory due to age with an n back task in order to investigate the neuroanatomical correlates of this modification.

Nyberg and collaborators in 2009 used an n back task with letters with three conditions (1, 2 and 3 back) and they used fMRI in order to see the differences due to age. Moreover, they divided the young participants into two groups depending on performance: one group was formed of high performing and the other one of low performing participants (Nyberg et al., 2009). The data showed the load effect: the increase of n was correlated with spreader activity in the brain; the areas involved in the task were related to the frontal-parietal network (Nyberg et al., 2009). In the parietal region the difference between groups was seen in the inferior parietal region, while in the frontal zone the difference was detectable in the left precentral region: while the young participants continued to have this zone activated, in the older subjects there was a decrease related to the increase in the working memory load (Nyberg et al., 2009). In the lowest level, the response of the elderly participants was higher than both the young groups; this response is probably due to a compensation mechanism; the same pattern was seen in the 2 back condition of the low young group, even if it does not reach statistical significance (Nyberg et al., 2002 in Nyberg et al., 2009). In addition, the left thalamus showed the same pattern (Nyberg et al., 2009). The parietal cortex seems to be related to the quantity capacity of the working memory (Nyberg et al., 2009). The frontal activity could represent the reallocation of resources in order to complete the task, maybe as a response to a suboptimal dopaminergic signalling (Backman et al., 2006 in Nyberg et al., 2009). Moreover, the age related changes seem to be dependent on striatal changes related to training and updating (Dahlin et al, 2008 in Nyberg et al., 2009).

Mattay et al. in 2006 used the same tool in order to investigate the changes in an n back task, with numbers as stimuli in three load conditions: 1, 2 and 3 back. The distribution of the activation in both groups during the task was similar: prefrontal cortex, pericingulate cortex, anterior cingulate and parietal (Mattay et al., 2006). In the one back condition the older participants had an higher activation in the regions mentioned above which were the same in the younger participants, while in 2 and 3 back conditions the prefrontal bilateral activation showed a decrease in the elderly (Mattay et al., 2006). The neuroanatomical response in aged participants is shaped like an inverted U, while the contrary pattern was seen in the younger participants (Mattay et al., 2006). The higher activation in 1 back in the older participants seems to represent a compensation mechanism, while the decrement of the activity during high load seems to be related to the behavioural results: the hypo frontal response is due to the fact that the task is beyond their capacity (Mattay et al., 2006).

Vermeji et al. (2012) used an n back task with letters as stimuli with a control condition and two load ones: 1 and 2 back. They used the NIRS technique, with two channels placed in the prefrontal cortex: one on the right and one on the left. The two channels showed different patterns, therefore they were analyzed separately; in younger participants, the left channel showed an increase in activation in line with the working memory load, while in the elderly both of them increased due to the increase in the n condition (Vermeji et al., 2012). The older participants showed a spreader activation caused by the compensation that appeared in all the experimental conditions (Vermeji et al., 2012).

1.4.3 Electrophysiological correlates of ageing in working memory

Ageing affects in different ways the evoked potential components and some studies, with n back or other paradigms, attempt to highlight this phenomenon.

Relative to the P2 component, there is no agreement about the aging effect. In some studies, it is related with a decrement of it due to age in the prefrontal channels (Pfefferbaum et al. 1984, Ford & Pfefferbaum 1991, in Amenedo & Diaz 1998; Anderer et al. 1996), while other authors report no change (Brown et al., 1983; Picton et al., 1984; Barrett et al., 1987; Iragui et al., 1993) in Amenedo & Diaz 1998) or an increment of this component due to age (Czigler et al., 1992 in Amenedo & Diaz 1998). The same is true for the latency. Some studies found an increment of it caused by age (Goodin et al., 1978; Picton et al., 1984; Iragui et al., 1993 in Amenedo & Diaz 1998), while others a decrement or no effect (Brown et al., 1983; Pfefferbaum et al., 1984; Barrett et al., 1987; Ford and Pfefferbaum, 1991 in Amenedo & Diaz 1998). In the study of Amenedo and Diaz (1998) with an oddball task, the P2 showed no change in the latency, while the amplitude was higher due to age in the frontal electrodes. In these electrodes, there was a clear effect of age: middle aged and elderly participants showed a clear linear effect at Fz (Amenedo & Diaz 1998). This increase in the amplitude at Fz could be attributed to a deficit of withdrawal of the attention from one stimulus that does not require such an amount of attention (Amenedo & Diaz 1998). The fact that this effect is found at Fz could be because the frontal region reaced to the interference caused by the irrelevant stimulus and inhibited the activity caused by habituation (Dempster, 1991; Dempster 1992; Van Zomeren & Brouwer, 1994 in Amenedo & Diaz 1998).

Anderen and colleagues (1996) used an oddball paradigm, similar to the one used by Amenedo & Diaz (1998). The latency in the P2 was affected by age only in the prefrontal electrodes: it increased because of age (Anderen et al, 1996). The amplitude showed a clear effect due to age too: it increased until the participants reached 60 years of age and then it decreased. Moreover, the distribution of this component was different between groups: the young participants showed greater P2 in the parietal regions, while in the older subjects it was frontally (Anderen et al, 1996). Finningan and colleagues (2011), during a working memory task (Sternberg task) found no difference due to age in the P2 in the prefrontal electrodes, while the amplitude was higher for the younger participants in the parietal site (Finningan et al., 2011). No effects in the latency were found, both in frontal and parietal electrodes (Finningan et al., 2011).

As already mentioned above, the P3 was the most studied component in the working memory topic and the same was true regarding the timing effect of aging. Regarding this component, studies that used the n back paradigm were found.

Frtusova, Phillips and Winneke (2013) used an n back paradigm with numbers as stimuli (they were presented acoustically) and the conditions were: control, 1 and 2 back. The P3 showed an effect of age: the amplitude was higher in the younger participants; the latency did not show any effect due to age (Frtusova, Phillips and Winneke, 2013). This result was consistent with other works published beforehand (Friedman, Simpson, & Hamberger, 1993; Vesco, Bone, Ryan, & Polich, 1993; Walhovd, Rosquist, & Fjell, 2008 in Frtusova, Phillips and Winneke, 2013).

Gajewsky and Falkenstein (2014) used an n back task with control and 2 back condition in order to see the effect of age on working memory. The P3a, found at Cz, showed an effect of age: it had higher amplitude in the older participants, in both the conditions (between them there was no difference) (Gajewsky and Falkenstein, 2014). Moreover, in the older participants it was clearly reduced when the load increased (Gajewsky and Falkenstein, 2014). Relative to the latency, it was slower in the older participants (Gajewsky and Falkenstein, 2014). The P3b, found at Pz, showed a reduction of the amplitude due to age and showed less difference between target and non target within this group (Gajewsky and Falkenstein, 2014). Finally, the latency was slower due to age (Gajewsky and Falkenstein, 2014). The P3a is related to turning the attention to the stimulus and to the voluntary aspect of the novelty perception (Daffner et al., 2005; Falkenstein et al., 1994; Friedman et al., 2001; in Gajewsky and

Falkenstein, 2014; Polich, 2007). The reduction in this component could be read as uncertainty in the selection of the response by the older participants (Gajewsky and Falkenstein, 2014). The P3b is related to the memory process and allocation of cognitive resources (Polich, 2007). It seems to be related to a slower response and also to less accuracy shown by the elderly participants (Gajewsky and Falkenstein, 2014).

Daffner and collaborators (2011) used a verbal n back task with three conditions: 0, 1 and 2 back. The older participants showed more amplitude in the P3 and this component manifested a different localization in the scalp: it was more anterior than that of the younger participants (Daffner et al., 2011). Regarding the latency, in the elderly it increased at the increase of n, while no change was found in the younger participants (Daffner et al., 2011). Compare to the younger, the elderly try to compensate by recruiting more resources in the frontal site (Daffner et al., 2011).

Wild-Wall, Falkenstein and Gajewski (2011) used an n back task with letters. The P3 was smaller in amplitude due to age. Younger participants showed a more pronounced P3 in the posterior part. The amplitude reduction is correlated with an ineffective maintenance of relevant information that leads a loss of it (Wild-Wall, Falkenstein and Gajewski, 2011).

In addition, the N3 working memory elicited component show an age effect, even if only two studies reported it.

Daffner et al. (2012) discovered, using a verbal n back task with three conditions: 0, 1 and 2 back, that only young participants generated this component in the frontal electrodes, while older subjects did not. This decline was found in other works and it is detectable when subjects perform a conflict task, an incompatible situation have to deal with a mismatch between expectation and behavioural performance (Willemssen et al., 2011; Beste et al., 2009; Mathewson et al., 2008; Themanson, Hillman, & Curtin, 2006 in Daffner et al., 2012). These functions seem to be related to the anterior cingulate cortex that due to age shows a reduction in tissue and in functional activity (Salat et al., 2009; Vaidya et al., 2007; Schultz et al., 1999 in Daffner et al., 2012).

Also West and Covell (2001) saw an effect of age in the N3 during a prospective task. Specifically, they found a dramatic reduction in this component in the frontal pole due to age. This supports the behavioural data found, that showed a decrease in accuracy and an increase in the reaction time in this group. This different pattern could explain those results, while there seems to be a functional impairment in a frontally mediated system that reduced the ability to retain the intention and not maintain it in an accessible state (West & Covell, 2001).

1.5 Aims of this thesis

Despite the large numbers of working memory studies in literature, less is know about the visuo-spatial sketchpad store, because most of them investigated the phonological loop. In the studies that investigated working memory correlates in adults, 30 studies investigated the phonological loop and only 8 the visuo-spatial sketchpad. Moreover, in the studies about ageing and working memory, 15 studies investigated the phonological loop and only one the visuo-spatial sketchpad. Finally, in this paper only behavioural correlates were investigated.

This thesis was carried out in order to fill this lack. In particular it had the aim to respond to three main questions. The fist one was related to when and how visuo-spatial working memory starts to be affected by age. In order to reply to this question one cross-sectional study was carried out with participants ranged from 20 to 80 years old. The second question was about the correlates of this changes, so adults and healthy elderly was tested during a visuo-spatial working memory task. In order to know in detail ageing effect behavioural, psychophysiological and hemodynamic correlates were recorded together. The last question was about how a pathology related to prefrontal cortex changes could influenced visuo-spatial working memory. In order to reply to this question we compared healthy elderly participants with Parkinson's disease patients.

Moreover, since is well-known that ageing is effected by both educational level and cognitive reserve, they were taken into account. In the first study, both educational level effect and cognitive reserve one were studied in ageing process. In the second and the third one the participants were selected with similar educational level and cognitive reserve. To take into account those two aspects was something new compared to the previous literature on working memory.

CHAPTER TWO

When and how ageing has an effect on visuo-spatial working memory. Behavioural correlates from adulthood to old age in an n back task: a cross-sectional study.

2.1 Introduction

Ageing is related to changes in cognitive functions. These modifications are due to the change in the morphology and biology of the neural structure. The volume of grey matter decreases because of age and this is a consequence of lower synaptic densities (Therry, 2000 in Hedden & Gabrieli, 2004). However, different regions of the brain respond in a different way to age: the prefrontal area, as well as the medial temporal one, show a decrease while the occipital cortex, for example, remains the same (Resnick et al., 2003; West, 2002 & Razz, in press in Hedden & Gabrieli, 2004).

Like the pattern of the decrement in the neural structure, some functions remain stable during time while others worsen. Working memory, processing speed and the recording of new episodes decrease, while short term memory, autobiographical information, semantic knowledge as well as emotional processes remain stable (Hedden & Gabrieli, 2004). In the Seattle Longitudinal Study - the biggest longitudinal study about ageing - researchers discovered that the effect of age becomes visible from 60 years onwards.

A part of the ageing studies in the literature focused on the changes in the working memory by using different experimental paradigms, among which the n back task (for a more detailed description see Chapter 1).

Most of the studies had the goal of investigating neural or electrophysiological brain modification due to age (Wild-Wall, Falkenstein & Gajewski, 2011; Daffner et al., 2011; Gajewski & Falkenstein, 2014; Missioner et al., 2004; Vemeij et al., 2012; Mattay et al., 2006; Nyberg et al., 2009). Only three of them had the sole goal of investigating the behavioural correlates of working memory in the ageing process (Van Gerven, 2008; Voelcker-Rehage, Stronger & Alberts, 2006; Vaughan et al., 2008).

Among the studies, one uses a modified version of the visuo-spatial n back task (Schmiedek, Li & Lindenberger, 2009), while all the others used letters or numbers as stimuli. (Wild-Wall, Falkenstein & Gajewski, 2011; Daffner et al., 2011; Gajewski & Falkenstein, 2014; Missioner et al., 2004; Vemeij et al., 2012; Voelcker-Rehage, Stronger & Alberts, 2006; Mattay et al., 2006; Nyberg et al., 2009; Van Gerven, 2008; Vaughan et al., 2008).

Regarding the conditions used: two studies compared the control condition and 2 back (high cognitive load) (Wild-Wall, Falkenstein & Gajewski, 2011; Gajewski & Falkenstein, 2014), one study used control, 1 (low cognitive load) and 2 back (Daffner et al., 2011), two used only high and low conditions (Missioner et al., 2004; Van Gerven, 2008) and one also made use of 3 and 4 back conditions (Vaughan et al., 2008).

Regarding the accuracies, all studies found a decrement due to age in the task that involved working memory, while the control condition did not show any difference (Vaughan et al, 2008; Van Gerven, 2008; Daffner et al., 2011). In some of these studies the differences were already present in the low condition of the task (Vaughan et al, 2008; Van Gerven, 2008; Daffner et al., 2011; Nyberg et al., 2009; Voelcker-Rehage, Stronger and Alberts, 2006). Differently, others found only differences in the highest working memory requirement trials (Mattay et al., 2006; Gajewski and Falkenstein, 2012; Wild-Wall, Falkenstein and Gajewski, 2011; Schmiedek, Li & Lindenberger, 2009).

Relative to the reaction time results, the majority of the studies found a decrease due to age in both low and high cognitive load conditions (Mattay et al., 2006; Missioner et al., 2004; Vaughan et al, 2008; Van Gerven, 2008). The same pattern was found in Gajewski and Falkestein's study (2012) and in Schmiedek, Li & Lindenberger's research (2009), in which only control and 2 back conditions were used, as well as in Wild-Wall, Falkenstein and Gajewski (2011), who only used the high cognitive load one.

Finally, only Vermeji and collaborators in 2012 did not find any differences due to age.

All of the studies were based on comparing two groups with different ages (Wild-Wall, Falkenstein & Gajewski, 2011; Daffner et al., 2011; Gajewski & Falkenstein, 2014; Missioner et al., 2004; Vemeij et al., 2012; Voelcker-Rehage, Stronger & Alberts, 2006; Mattay et al., 2006; Nyberg et al., 2009; Van Gerven, 2008; Vaughan et al., 2008). In the young group, the age of the participants in different studies ranged between 18 and 32 (Wild-Wall, Falkenstein & Gajewski, 2011; Daffner et al., 2011; Gajewski & Falkenstein, 2014; Missioner et al., 2004; Vemeij et al., 2012; Voelcker-Rehage, Stronger & Alberts, 2006; Mattay et al., 2006; Nyberg et al., 2009; Van Gerven, 2008; Vaughan et al., 2008; Schmiedek, Li & Lindenberger, 2009). Regarding the old group, in two studies there were participants that were younger than 60 (Wild-Wall, Falkenstein & Gajewski, 2011; Mattay et al., 2006), while in the other they were older (Schmiedek, Li & Lindenberger, 2009 Gajewski & Falkenstein, 2014; Missioner et al., 2004 Vemeij et al., 2012; Mattay et al., 2006; Nyberg et al., 2009; Van Gerven, 2008; Voelcker-Rehage, Stronger & Alberts, 2006).

Regarding the recruitment of the participants, Hedden and Gabrieli (2004) showed that participants from senior centres as well as people that come in universities to participate, are not representative enough of the population. In the first case, the probability to test participants with pathologies or diseases is higher. On the other hand, the other type of participants recruited, could be not representative enough of the population.

In many studies, participants were divided into two groups based on their performance. Normally, subjects in the upper quartile category of data distribution (they have the best results) are the high performers, while the participants that are in the lower quartile are the low performers (Conway et al., 2005). This way of categorizing the data is not correct from a statistical point of view for several reasons; the first one being that some information is lost and consequently the statistical power decreases. Another reason is that the results of participants inside each group are incorrectly regarded as being equivalent. Finally, they can also be classified in an erroneous way (Conway et al., 2005).

In the visuo-spatial and spatial tasks, since the 1970s, it has been reported that males and females perform differently. Not all studies have found this result, probably due to the experimental characteristics per se, but those who did, found effects in both behavioural and neuroanatomical correlates. In those studies males outperformed females (Hampson & Kimura, 1992; Linn and Petersen 1985; Maccoby & Jacklin 1974; Voyer et al. 1995 in Moffat, Hampson & Hatzipantelis, 1998) and this seems to be related in particular to orientation and spatial visualization (Borich and Bauman, 1972; Ekstrom et al. 1976; Michael et al 1951 in Moffat, Hampson & Hatzipantelis, 1998). Since this difference is also present in other mammalian species (Dawson, 1972; Gaulin and Fitzgerald, 1986; Roof and Havens 1992; Stewart et al. 1975; Williams and Meck 1991; Williams et al. 1990 in Moffat, Hampson & Hatzipantelis, 1998), some authors hypothesized evolutionary theories. Some of them referred to the fact that the males had to control and defend their territory from other male adversaries (Gaulin & Fitzgerald, 1986; 1989 in Moffat, Hampson & Hatzipantelis, 1998). Others affirmed that the difference is present because the males were the ones who explored the territory in order to find food for their hunter-gatherer tribes (Kolakowski and Malina 1974; Silverman & Eals 1992; Watson & Kimura 1991; Sherry & Hampson 1997 in Moffat, Hampson & Hatzipantelis, 1998).

Astur, Ortiz and Sutherland (1998) found that in a virtual reality task in which the participants had to swim from a starting point to an end one by passing through a maze, males took less time and made fewer errors than females. The same results were found in Moffat, Hampson & Hatzipantelis (1998), in which participants had to find a way out of a maze; males were faster and made less errors than females and differences were also found in three orientation cognitive tests (Vandenberg Mental Rotations Test, Guilford-Zimmerman Spatial Orientation Test and Money Road Map Test). Moreover, there was a positive correlation between the maze performance and the results in the cognitive tests (Moffat, Hampson & Hatzipantelis 1998). The same pattern was not found in verbal tests, even if females reported more words than their male counterpart (Controlled Oral Word Association Test and vocabulary scores of the Wechsler scale) (Moffat, Hampson & Hatzipantelis, 1998).

The neural correlate of the difference between males and females in visuo-spatial tasks showed that during a virtual reality task, in which participants had to move inside a maze, women activated the right parietal and right prefrontal areas more, while men activated the left hippocampal one (Grön et al., 2000).

Regarding the n back task, only one study (Schmidt et al, 2009) compared both behavioural and neural correlates (collected by fMRI) of male and female participants ranging between 18 and 58 years of age and no differences were found. The explanation could be in the stimuli used, since they were letters.

A visuo-spatial n back one could shows some differences between males and females and it would be interesting also to see if these differences (if any) remain stable or change from adulthood to an elderly age.

Despite the large number of studies carried out regarding working memory, less is known about the age range between 30 and 50 years. In order to have a more complete picture of the working memory ageing phenomenon, a study that takes into consideration ages ranged between 20 and 80 is needed. Regarding the paradigm, the best option seems to be a visuo-spatial n back one, for two reasons. The first one being that only one study was carried out with this paradigm (while all the others used letters or numbers as stimuli); the second is that the task is language free. A language-free task is more useful because nowadays as well as in the future, many of the participants tested could come from other countries and this may have an effect on the results.

Another goal of this experiment was to also establish when the working memory starts to decrease due to age; this was an open question, since with the experimental design of the studies that came before (the sole comparison between young and old) it was not possible to answer this question.

Moreover, in order to avoid the confounding nature due to the recruitment of participants that came in universities as well as participants tested at home, the solution used was to test both (Hedden & Gabrieli, 2004).

Relative to the analysis of data, the participants were not divided into high and load performers, due to the reasons explained earlier (Conway et al., 2005).

Finally, based on the difference found in the literature (Astur, Ortiz and Sutherland, 1998), males were compared with females. Furthermore, due to the lack of knowledge about this effect of ageing, this hypothesis was also tested to establish what these differences actually were.

2.2 Method

2.2.1 Participants

The sample consisted of 134 participants with ages ranging between 19 and 81 years; all of them were volunteers. The participants, due to the reasons explained before, were recruited both at home as well as at university laboratories.

Inclusion criteria were: self-report of healthy status and normal or correct-to-normal vision. Exclusion criteria were: history of neurological disorders, psychiatric illness, report of depression or anxiety, use of psychotropic medications, a score in MMSE below 24 (Folstein, Folstein, & McHugh, 1975), a score in ANT below 14 (Sager, Hermann, LaRue & Woodard, 2006) and the consumption of more than 15 standard drink unit for women and 20 for men per week.

The data of 7 participants had to be excluded from the analysis; one because of a diagnosis of anxiety and one of depression, two because of stroke and four because of a score in MMSE below 24. The final sample consisted of 128 participants; the characteristics of the sample are reported in Table 2.

Years	Total number	Males	Females	Educational level					
				PhD/ Specialization	Master degree	Bachelor degree	High school degree	Middle school degree	Elementary degree
20-29	29	15	14	0	5	6	16	2	0
30-39	18	8	10	0	7	4	3	4	0
40-49	22	7	15	0	3	1	11	7	0
50-59	23	7	16	1	4	1	6	11	0
60-69	21	11	10	1	1	0	11	8	0
70-79	15	9	6	0	2	0	2	0	11
Total	**128**	**57**	**71**	**2**	**22**	**12**	**43**	**32**	**11**

Table 2 Characteristics of the sample. Number of participants, gender and educational level for each decade.

2.2.2 Task, tests and data collected

The task was an adapted version of the visuo-spatial n back task from Cui et al. (2011) and Haberecht et al. (2001). The percentage of target presence was decided in reference to the Jaeggy et al. (2010) study; consequently, the target was present in 33% of the task. The task was administered on a personal computer with a 17-inch display; the resolution of the screen was configured at 1024x768 pixels and using E-prime software (Psychology Software Tools, Pittsburgh, PA). Participant's responses consisted in pushing the letter "k", which was covered with a white adhesive, as the instructions were to press "the white button". The response button was different from the one that participants had to press throughout the task in order to begin the task and to finish the breaks; in those cases, they had to press the space bar.

The stimulus was the letter "O", 66x156 pixels large and in each trial it could appear in different positions, since a 9-part grid divided the entire screen; each part of the grid was 340x255 pixels big. The stimulus lasted for 1500 milliseconds and there was a constant pause between stimuli intervals of 500 milliseconds in which only the grid was displayed. The task consisted in remembering the position of the letter "O" because if it appeared in the same position as the trial before (1 back) or in two trials before (2 back) the participants had to respond. A control condition was also present (0 back) in which participants pushed the response button if the letter "O" appeared in the central part of the grid (Figure 2). The control condition was administrated between the other two conditions; in total there were 6 blocks for 2 back as well as 1 back and double the amount for the control condition. In the one back the order of the task was the following: 1 back-0 back-1 back-0 back-1 back-0 back-1 back-0 back-1 back-0 back-1 back-0 back; and in the two back it was: 2 back-0 back-2 back-0 back-2 back-0 back-2 back-0 back-2 back-0 back-2 back-0 back. The order of the 1 and 2 back blocks was counterbalanced between the participants. Before the main blocks of the experiment, there was a practice block, in which participants performed the task until they understood it completely. Otherwise, they had the possibility of repeating the practice block if they felt unsure about proceeding. Before the initialization of each block, the participant was prompted with a message containing the instructions for the block that was about to follow.

Only the 0, 1 and 2 back conditions were used, since some previous works showed that participants gave up when the cognitive load was higher (Brower et al., 2012; Izzetoglu et al 2007, Ayaz et al 2007).

Each block was formed of 23 stimuli, 7 of which were targets and 16 were non targets, for a total of 552 stimuli, 168 of which were targets and 384 non targets.

Finally, between each block, there was a break in which they received feedback about their previous performance (means of the reaction time and percentage of correct responses). Participants were encouraged to respond both fast and correct and to take longer breaks between blocks if they felt tired.

The task lasted 25 minutes.

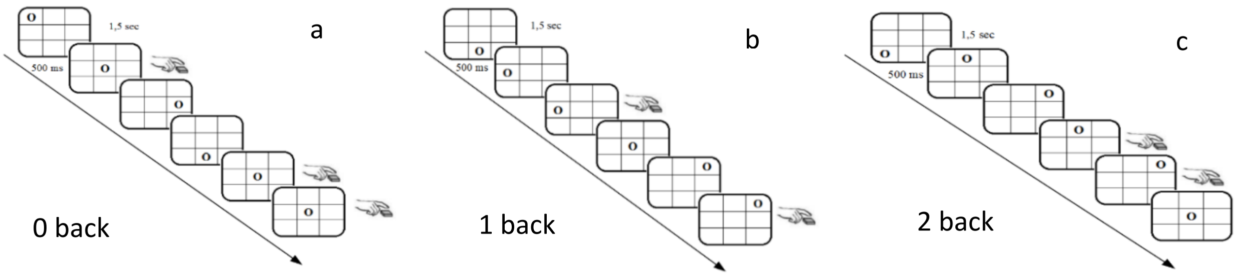


Figure 2 The visuo-spatial n back task. a) 0 back condition b) 1 back condition c) 2 back condition

The MMSE (Folstein, Folstein, & McHugh, 1975) is one of the most famous tests used to investigate the cognitive decline (The test is reported in the appendix). It is used with participants from 65 years and it is well suitable both in clinical and experimental contexts. The MMSE is formed by 30 items. It investigated: spatial and temporal orientation, learning and recall of three common names, attention (the task consist in spell backword a word), calculation (the task consist in count backword 5 times from 100, subtracting 7 each time), comprehension of both written and oral commands, writing and constructional apraxia. The sum of the correct responses gives the result, in which a correction is applied based on age and level of education of the Italian population. The cut-off is 24 (Folstein, Folstein, & McHugh, 1975).

The ANT (Sager, Hermann, LaRue & Woodard, 2006) is a verbal fluency test in which participants had to report in 60 seconds all the animals that they could recall (the test is reported in the appendix). The sum of the animals reported is the final score and the cut-off is 14 (Sager, Hermann, LaRue & Woodard, 2006).

The Cri-q (Nucci, Mapelli & Mondini, 2011) is a test that evaluates the cognitive reserve (Stern, 2009) by using information regarding the adult life of the person (the test is reported in the appendix). It is a semi-structured interview formed of three main parts. The first one is related to educational level and takes into account both the number of school years and the courses take. The second one is based on work activities and it takes into consideration all the jobs that the person did and still do. The last one, related to the leisure time, investigated all the activities that the person did and still does in the free time. This part takes into account fixed activities (such as caring for pets and children), activities with an annual frequency (such as journeying and book reading), activities with monthly frequency (such as social activities and volunteering) as well as weekly activities (such as driving or reading newspapers). It gives four different scores: one is about the educational level, one is about career, one is about leisure time and the sum of them is the cognitive reserve. Different scores are related to different grades of cognitive reserve: low (less than 70), medium-low (between 70 and 84), medium (between 85 and 114), medium-high (between 115 and 130) and high (more than 130) (Nucci, Mapelli & Mondini, 2011).

2.3 Procedure

All the tests were administrated during the same session; the order was the same for all the participants, except for the n back, in which two versions were presented in order to create a counterbalance between participants. Before starting participants read and signed the informed consent; they were unware about the aim of the study.

The visuo-spatial n back was the first task administered, in order to avoid possible fatigue effects. The participants were seated in front of the screen, 50 cm away from it, in a quiet room with adequate luminosity. After the n back task, MMSE, ANT and CRIq data was collected and the questions about the healthy status were asked (the tests are reported in the appendix).

2.4 Results

Due to the characteristics of the data, a generalized mixed linear models analysis was applied; it is used in different fields, such as general science, medicine and engineering (Faraway, 2006; Fielding & Goldstein, 2006; Gilmour, Thompson, & Cullis, 1995; Goldstein, 1995; Pinheiro & Bates, 2000; Snijders & Bosker, 1999 in Baayen, Davidson & Bates, 2008). This type of analysis combines the two different models together, one being the linear mixed model (in which it is possible to take into account random effects) and the other one being the generalized mixed model (in which it is also possible to work with non-normal distributed data) (Bolker et al., 2008).

The most important advantage of generalized mixed linear models is that it is possible to consider each trial as an observation, instead of taking into consideration only the mean of the conditions of each subject. Therefore, in this experiment, instead of considering the means of each condition in the 128 participants we had 70656 observations. In this manner statistical power increases. Moreover, with generalized mixed linear models, it is possible to take into account the random effect; i.e. with this function it is possible to keep out the confounding characteristics of the single subject (such as cohort effects) (Baayen, Davidson & Bates, 2008). Another important advantage of this method is the possibility to use more than one predictor simultaneously (Baayen, Davidson & Bates, 2008).

The analyses were done with the package lme4 (Bates, Maechler & Bolker, 2012) by r software (R Development Core Team, 2010).

For both accuracy and reaction times, the same steps were followed. First, it was tested whether there was one or more fixed effects. Then, for each hypothesis, different models with the fixed effect and with different variables were created. The models contained one or more variables as well as interactions between them. Finally, the different models were compared to each other in order to find which model or models better explained the phenomenon, giving the best description of the data (Wagenmarkers & Farrell, 2004). One suitable and widely used method is the Akaike information criterion (Akaike, 1973, 1974, 1978, 1979, 1983, 1987; Bozdogan, 1987; Burnham & Anderson, 2002; Parzen, Tanabe, & Kitagawa, 1998; Sakamoto, Ishiguro, & Kitagawa, 1986; Takane & Bozdogan, 1987 in Wagenmarkers & Farrell, 2004; Dayton, 2003). It is a number that gives an estimation of the information lost; the less information lost, the smaller the number is. In order to compare models, we used an Anova analysis between them and if it showed a p value less than .05, the best model was chosen by the lowest AIC (Wagenmarkers & Farrell, 2004; Dayton 2003).

Regarding the models tested, the age, the cognitive reserve, the conditions (control, low and high cognitive loads) as well as the cognitive functioning and semantic category fluency results were analysed.

The level of education was not taken into account, since it presented collinearity with age. Collinearity is a phenomenon that happenes when two or more predictors are highly correlated. This has negative effects on the analysis of the data. The first one is that when estimating the models, the relation between variables will not be taken into account and this is hiding the real effects. Moreover, the collinearity reduces the variability of the predictor and, as a consequence, its influence.

In this study educational level negatively correlated with age [$r=-.513$, $N=128$, $p=.000$]. For the disadvantages of the collinearity only one predictor i.e. age was taken into account.

2.4.1 Accuracy results

The analysis regarding the random effect showed that only the subject had this effect, while the block, the trial and the stimuli did not. Therefore, the random effect of the subject was taken into account in each model designed.

Condition results

Cognitive load (0, 1 and 2 back) had effect on the accuracy results (AIC=5247.1; AIC null model=6330.7, p<.001) (Figure 3).

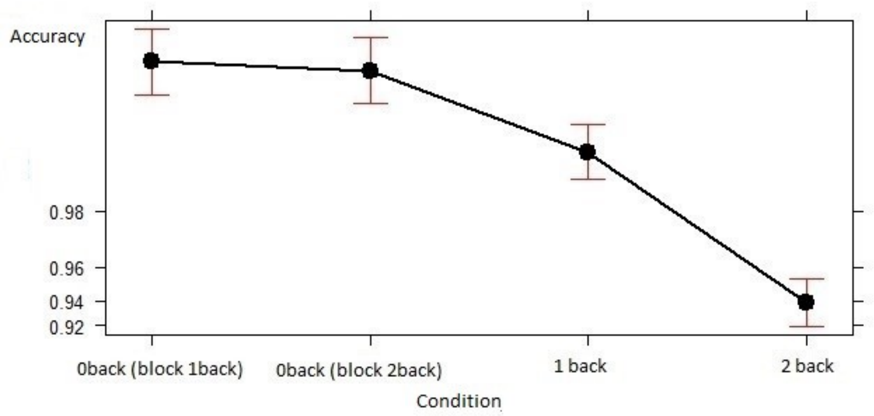


Figure 3 The decrement in the accuracies (y axis) due to the increase in the cognitive load (x axis). The black dots represent the means of the accuracies in the three conditions and the red lines represent the 95% confidence interval, while the black line the effect per se.

Gender results

Gender had not effect on accuracy results (AIC=5249.1; AIC null model=6330.7, p=.880).

Age results

Participants ranged 20-30 years were not taken into account because the less variance within this group caused not convergence in the model (Bates, Kliegl, Vasishth & Baayen, 2015). Both age (AIC=5791.6; AIC null model=5811.0, p<.001) and decade (AIC=6290.5; AIC null model=6330.7, p<.001) had effects on the accuracy (Figure 4, 6a and 6b).

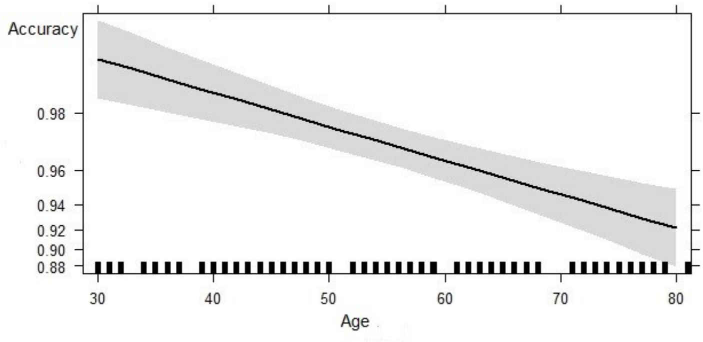


Figure 4 The age effect (y axis) on accuracies (x axis). The black squares represent the age of the participants, the black line the effect per se and the grey bar the confidence intervals.

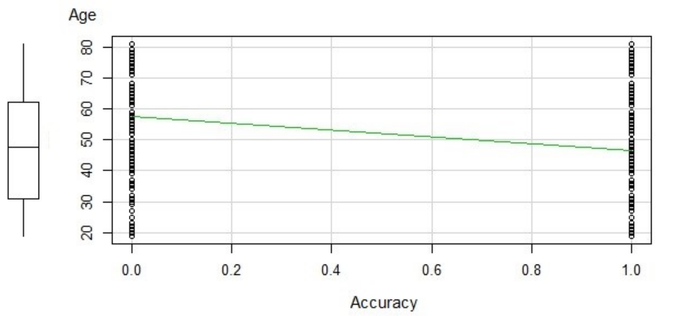


Figure 5 The accuracy (y axis) starts to decrease at 57.49 years of age (x axis).

Moreover, a model that has an accuracy of 0 was created and by doing this it was possible to see that age starts to have an effect on accuracy at 57.49 years of age (Figure 5).

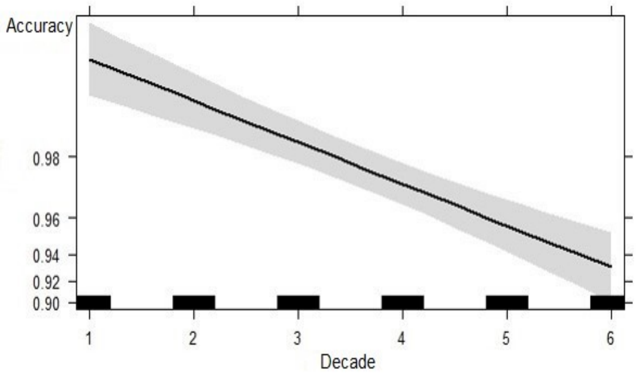


Figure 6a The decade effects (y axis) on accuracies (x axis). The black rectangles represent the decades, the black line the effect per se and the grey bar the confidence intervals.

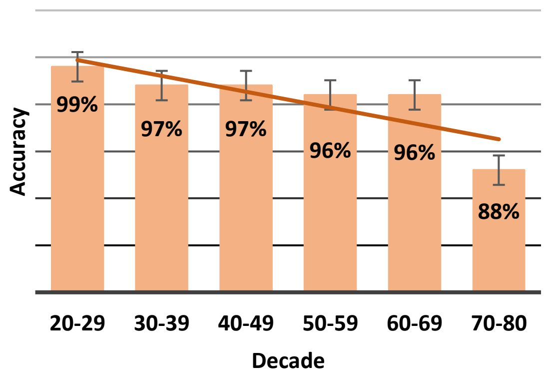


Figure 6b The decades effect (y axis) on accuracies (x axis). Each column represent the accuracy of one decade.

Age and cognitive loads had both effect (AIC=4741.8, AIC age model=5791.6, $p<.001$; AIC cognitive loads model=4761.7, $p<.001$); but independent each other (no interaction between these two factors were found).

Cognitive reserve results

The different scores of the cognitive reserve test showed different results.

The total cognitive reserve score influenced the accuracy data found (AIC=6304.0, AIC null model=V, p=.022) (Figure 7).

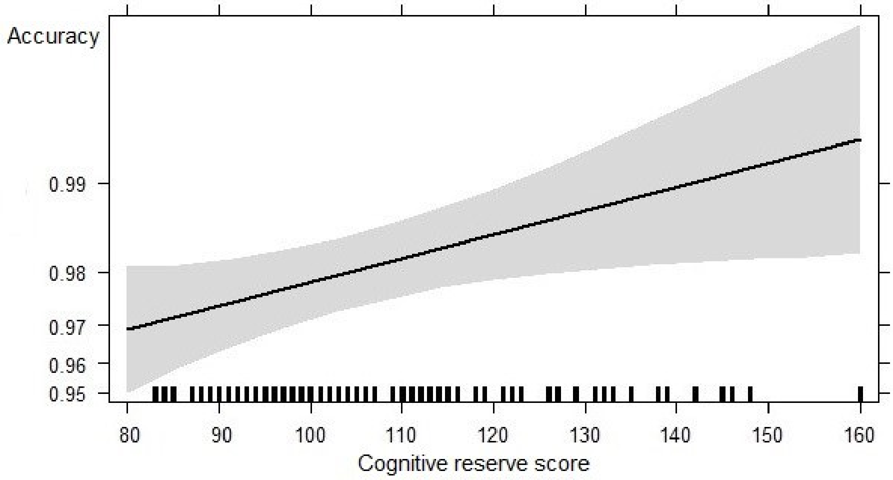


Figure 7 The cognitive reserve effect (y axis) on accuracies (x axis). The black rectangles represent the cognitive reserve score, the black line the effect per se and the grey bar the confidence interval.

Both age and total cognitive reserve score (AIC=5751.1, AIC age model=5768.7, p<.001) explained the data found, but those two effects are independent each other. The same was true for the cognitive load and age effects (AIC=4727.9, AIC cognitive load model=4738.9, p<.001)

The cognitive reserve related to educational level showed an effect on accuracy results (AIC=6285.7, AIC null model=6307.3, p<.001) (Figure 8). Age as an effect on accuracy effects, but those two effects were independent each other (AIC=5753.0, AIC age model=5768.7, p<.001).

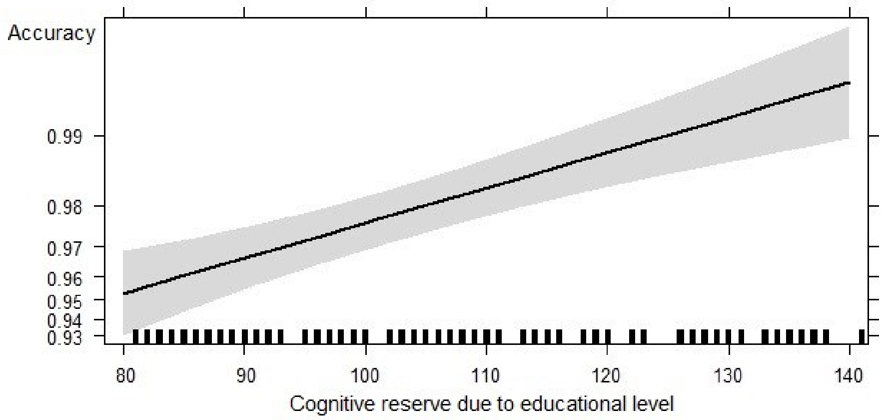


Figure 8 The cognitive reserve due to education effect (y axis) on accuracies (x axis). The black rectangles represent the cognitive reserve due to educational level results, the black line the effect per se and the grey bar the confidence intervals.

Finally, both cognitive reserve due to job (AIC= AIC=6307.4, AIC null model=6307.3, p=.176) and cognitive reserve due to leisure time (AIC=6308.5, AIC null model=6307.3, p=.399) did not explain the data.

Cognitive functioning results

The MMSE results had a positive effect on the accuracy results (AIC=5495.3, AIC null model=5516.4, p<.001) (Figure 9). Age as well had an effect on results found (AIC=5177.7, AIC age model=5181.2, p=.020) but the effect of it and of MMSE score were independent for each other.

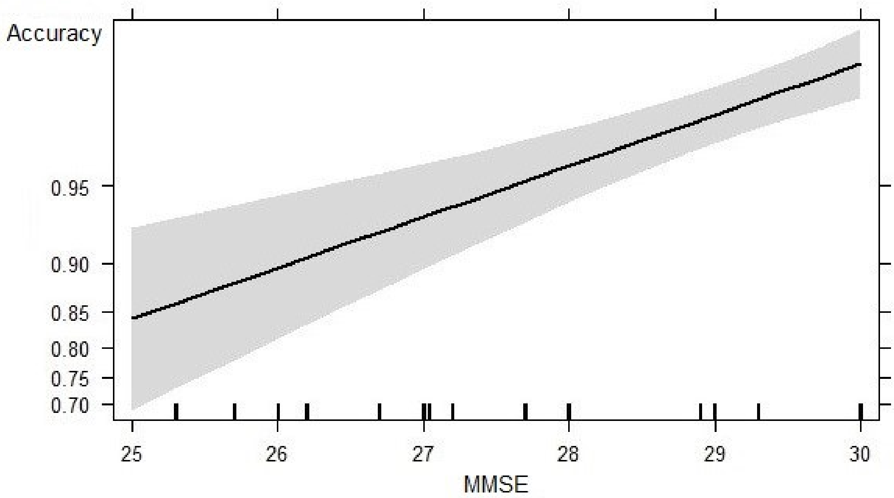


Figure 9 The MMSE (y axis) on accuracies (x axis). The black rectangles represent the MMSE results, the black line the effect per se and the grey bar the confidence intervals.

Semantic category fluency results

No effects of the ANT results were found.

2.4.2 Reaction times results

The reaction times curve showed a clearly screw to the right. For that reason, a logarithmic transformation was applied to them in order to have a distribution closer to the Gaussian one.

The possible random effects were tested. Among them only subject showed a random effect, while trial, block and stimuli did not. For that reason, the subject was taken into account as a random one in the models tested.

Condition results

The cognitive loads had an effect on the reaction times (AIC=7886.4, null model=8428.4, p<.001) (Figure 10).

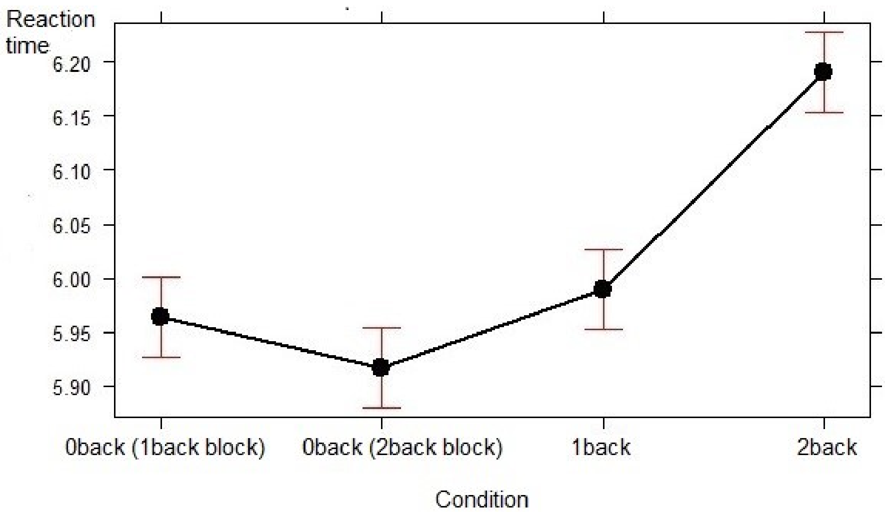


Figure 10 The increment in the reaction time (y axis) due to the increase in the cognitive load (x axis). The black dots represent the means of the reaction times in the three conditions and the red lines represent the 95% confidence intervals, while the black line represent the effect per se.

Gender results

Males were faster than female (AIC=8423.7, AIC null model=8428.4, p=.011) (Figure 11). This effect was found together with age (AIC=8371.1, AIC age model=8423.7, p<.001) and cognitive load ones

(AIC=7882, AIC cognitive load=8423, p<.001), but all of them were independent to each others (no interrelation were found).

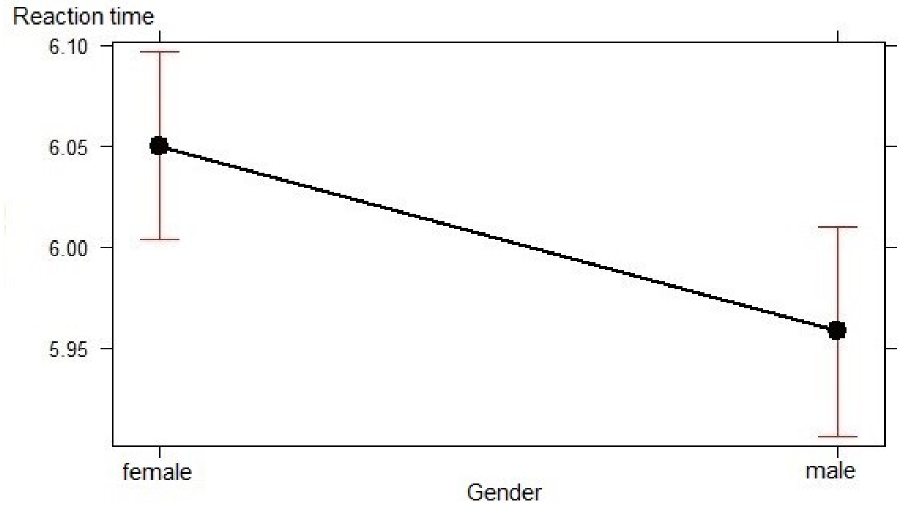


Figure 11 The effect of gender (x axis) on the reaction times (y axis). The black dots represent the means of the accuracies in the males and females and the red lines represent the 95% confidence interval, while the black line represent the effect per se.

Age results

Age had effect on reaction time results (AIC=8380, AIC null model=8428.4, p<.001) (Figure 13). A model that has a reaction time of 0 was created and by this was possible to see that age starts to have an effect on reaction time at 34.47 years (Figure 14).

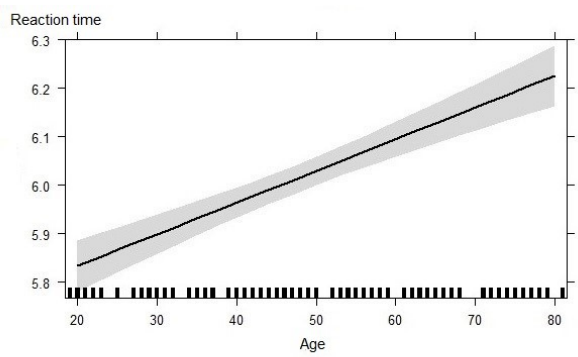


Figure 13 The age effect (y axis) on reaction time (x axis). The black rectangles represent the participants age, the black line the effect per se and the grey bar the confidence interval.

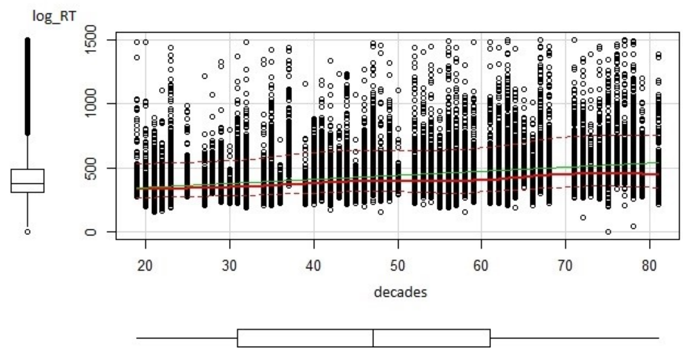
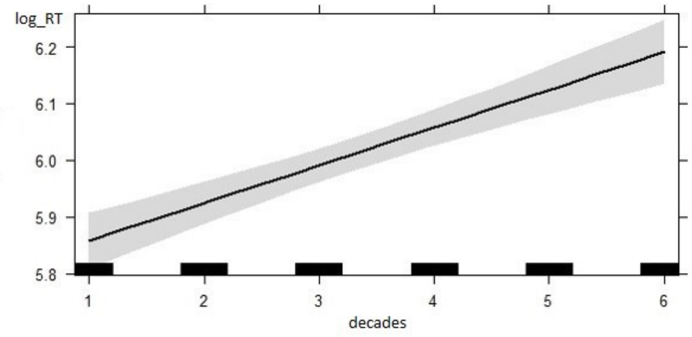


Figure 14 The reaction times (y axis) start to decrease at 57.49 years of age (x axis).

Similarly to age, decades explained the reaction time results (AIC=13346.98, AIC null model=15453.91, p<.001) (Figure 15a, 15b).



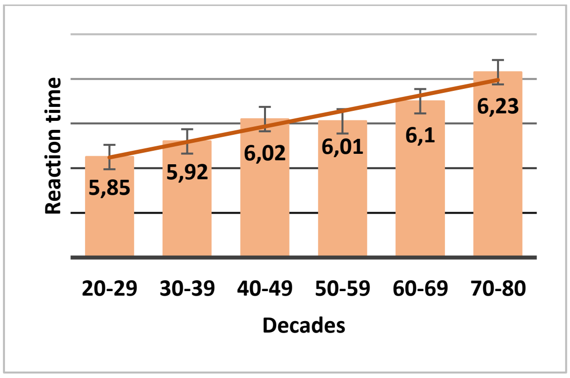


Figure 15a The decade effect (y axis) on reaction time (x axis). The black rectangles represent the decades, the black line the effect per se and the grey bar the confidence interval.

Figure 15b The decade effect (y axis) on reaction time logarithmically transformed (x axis). Each column represent the reaction time result of one decade.

Moreover, an interaction between age and cognitive loads were found (AIC=7825.5, AIC age and cognitive loads model=7836.2, p<.001) (Figure 16).

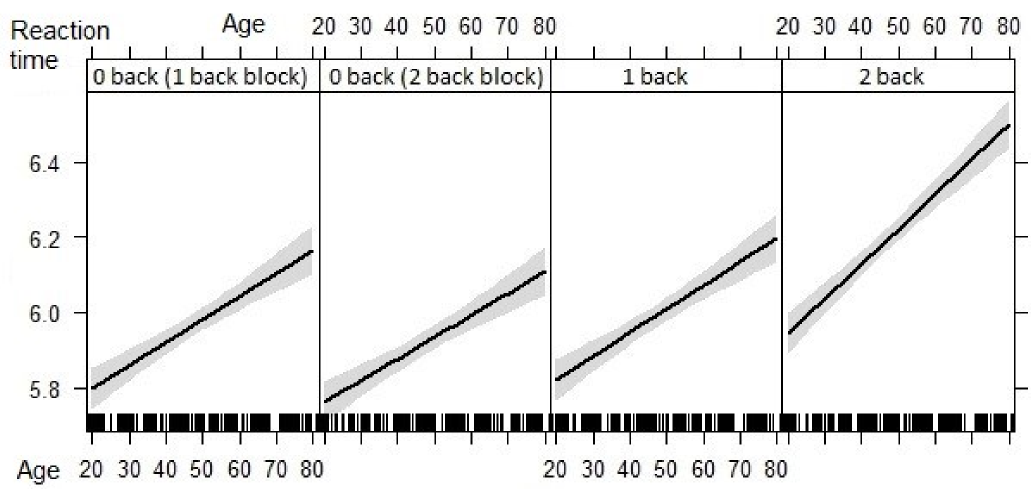


Figure 16 The interaction between reaction times (x axis) and age (y axis), in the control conditions, 1 back and 2 back.

The same results were found regarding the decade factor (AIC=5741.2, AIC decade and cognitive loads model=8381.4, p<.001) (Figure 17).

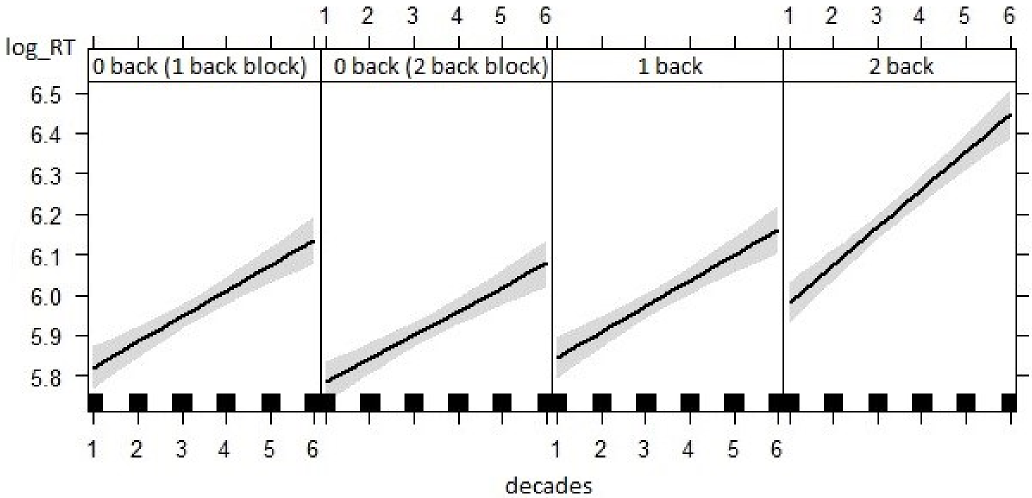


Figure 17 The interaction between reaction times (x axis) and decade (y axis), in the control conditions, 1 back and 2 back.

Cognitive reserve results

The total cognitive reserve score did not explained the results found (AIC=8363.4, AIC null model=8361.6, p=.670).

Differently, the cognitive reserve due to educational level had an effect on reaction times (AIC=8358.1, AIC null model=8361.1, p=.018) (Figure 18).

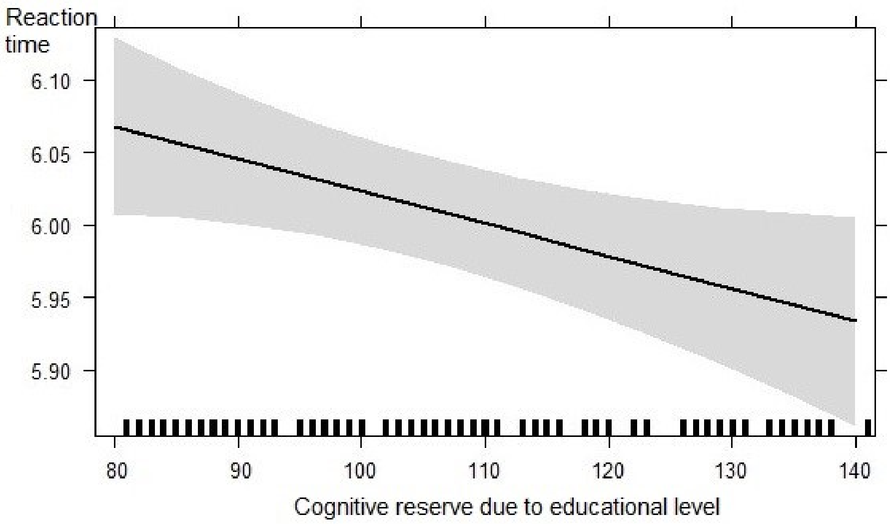


Figure 18 The cognitive reserve due to education level (y axis) effect on reaction time logarithmically transformed (x axis). The black rectangles represent the cognitive reserve due to educational level results, the black line the effect per se and the grey bar the confidence interval

Finally, an interaction between cognitive reserve due to educational level and cognitive loads was found (AIC=5789.9, AIC cognitive reserve due to educational level and cognitive loads=7819.2, p<.001) (Figure 19).

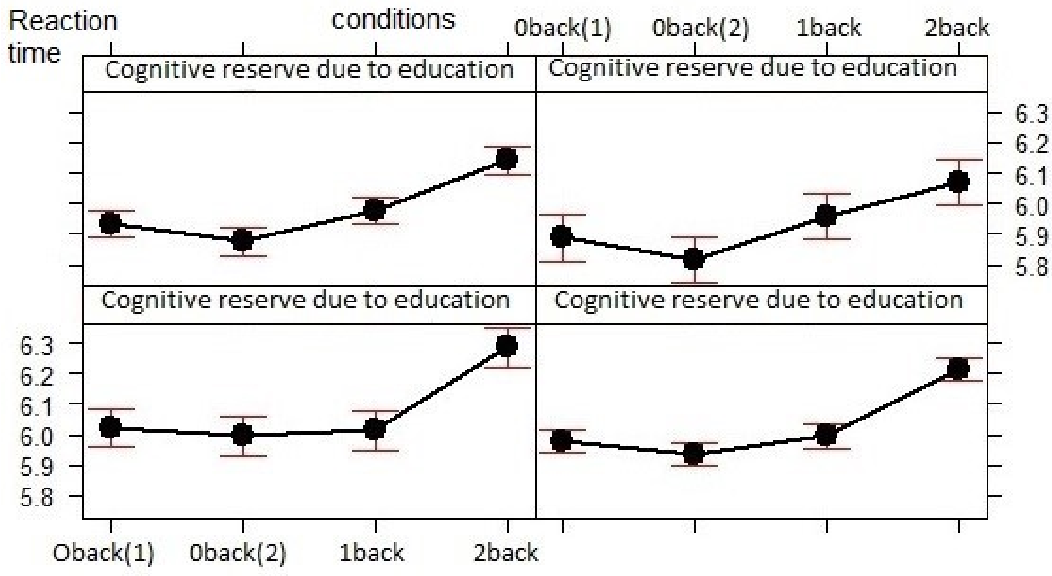


Figure 19 The figure shows the interaction between the conditions (x axis) and the cognitive reserve due to the education in the reaction times (y axis).

The cognitive reserve due to the job did not explained the reaction times found (AIC=8363.3, AIC null model=8361.6, p=.559).

Finally, the cognitive reserve due to leisure time had an effect on reaction times (AIC=8354.3, AIC null model=8361.1, p=.002) (Figure 20).

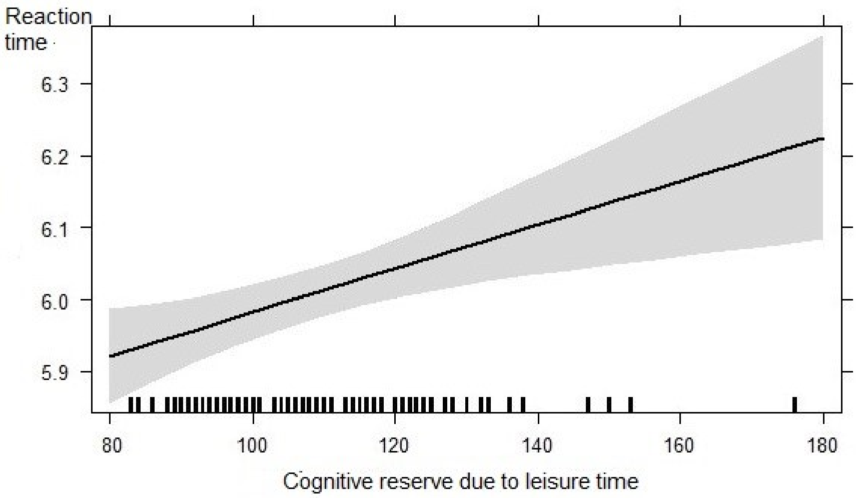


Figure 20 The cognitive reserve due to leisure time (y axis) on reaction time (x axis). The black rectangles represent the results, the black line the effect per se and the grey bar the confidence interval.

Both age and cognitive reserve had effects on reaction times, but they were independent to each other (AIC=8314.7, AIC age model=8361.6, p<.001).

Lastly, an interaction between cognitive reserve due to leisure time and cognitive loads was found (AIC=7804.8, AIC cognitive reserve due to leisure time and cognitive loads=7819.2, p=.003) (Figure 21).

Cognitive functioning results

The MMSE scores explained the reaction times results (AIC=7172.1, AIC null model=7200.9, p<.001) (Figure 21).

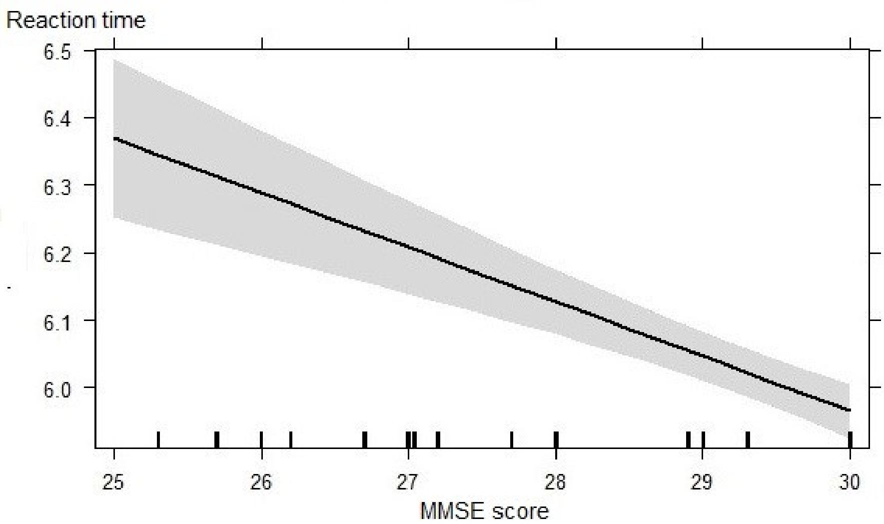


Figure 21 The MMSE score effect (y axis) on reaction time (x axis). The black rectangles represent the results, the black line the effect per se and the grey bar the confidence interval.

Moreover, MMSE and age had both an effect on reaction times, but they were independent for each other (AIC=7159.9, AIC age model=7167.6, p=.002). The same was true for the cognitive loads (AIC=5336.3, AIC null model=5306.4, p<.001).

Category semantic fluency results

The ANT scores had an effect on reaction times (AIC=8269, AIC=8285, p<.001) (Figure 22).

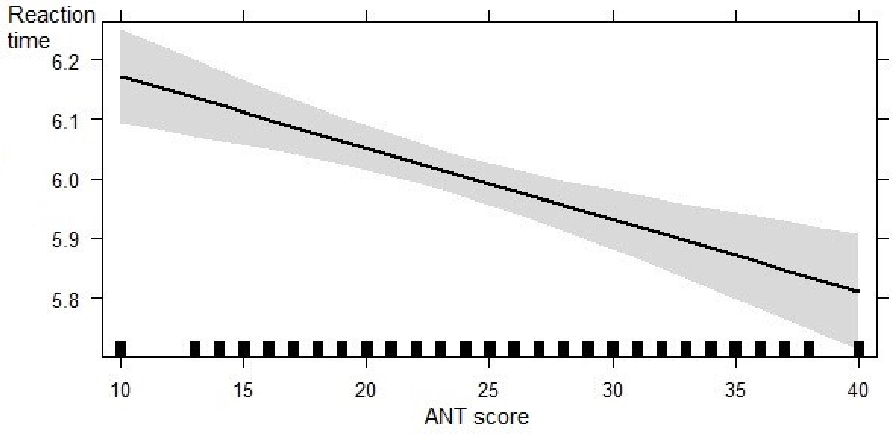


Figure 22 The ANT scores effect (y axis) on reaction time (x axis). The black rectangles represent the ANT score, the black line the effect per se and the grey bar the confidence interval.

Moreover, ANT score and age had both an effect on these results, but they were independent from each other (AIC=8236.6, AIC=8269.0, p<.001).

Finally, the ANT scores and the cognitive loads showed an interaction (AIC=5775.2, AIC=5822.8,p<.001) (Figure 23).

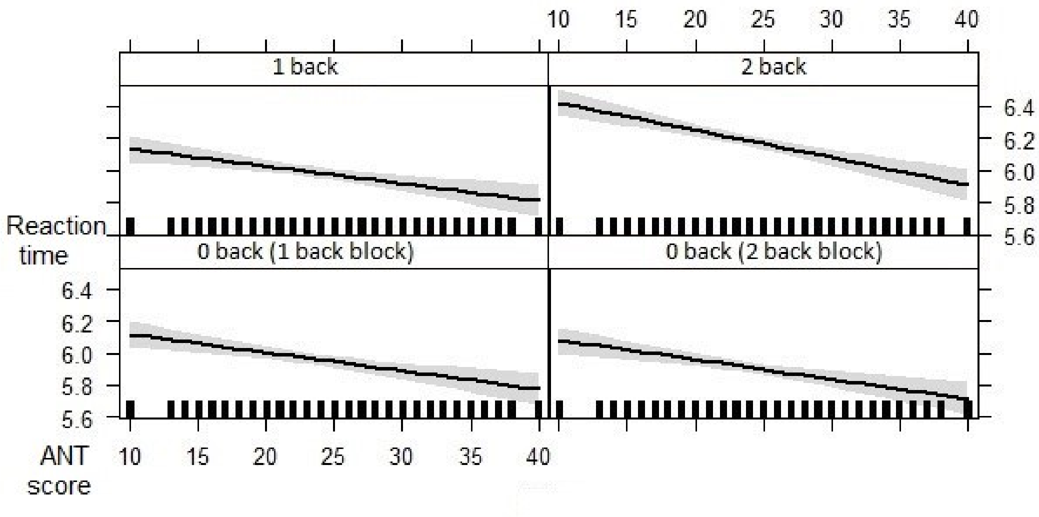


Figure 23 The interaction between ANT score (x axis) on reaction times (y axis) in different conditions; in the upper panels the low and high cognitive load conditions and in the downer the control one.

2.5 Discussion

In both accuracy and reaction time results, there was an effect of the cognitive load conditions of the task. As expected, increased working memory load resulted in an increase in the reaction time and a decrease in accuracies. This result is consistent with previous studies (Ragland et al., 2002; Chen, Mitra & Schlaghecken, 2008; Chen & Mitra, 2009; Raemae et al., 2001; Spronk & Jonkman, 2012; Tanaka et al., 2012; Leon-Dominguez, Martin-Rodriguez & Leon-Carrion, 2015; Alain et al., 2009; West, Bowry & Krompinger, 2006).

As expected, consistent with previous studies, age has an effect on behavioural correlates: reaction time increased with the increase of age (Mattay et al., 2006; Missioner et al., 2004; Vaughan et al, 2008; Van Gerven, 2008; Gajewski & Falkestein, 2012; Schmiedek, Li & Lindenberger , 2009; Wild-Wall, Falkenstein & Gajewski, 2011) and accuracy decreased (Vaughan et al, 2008; Van Gerven, 2008; Daffner et al., 2011; Nyberg et al., 2009; Voelcker-Rehage, Stronger and Alberts, 2006; Mattay et al., 2006; Gajewski and Falkenstein, 2012; Wild-Wall, Falkenstein and Gajewski, 2011). Those results showed that the same decrement due to age in the verbal working memory part is no different from the one in the visuo-spatial one; regarding this, the only study that used a similar paradigm found the same pattern (Schmiedek, Li & Lindenberger, 2009). This result allows the use of the visuo-spatial working memory task in future clinical and experimental contexts, with the advantage of having a language free task.

Regarding the effect of age and working memory load, the results showed that the accuracy and reaction times found both explain the data. In the accuracy results, those effects are independent from each other (similar to Vaughan et al, 2008; Van Gerven, 2008; Daffner et al., 2011; Nyberg et al., 2009), while with regard to the reaction times there was also an interaction effect between age and condition (Gajewski & Falkestein, 2014; Daffner et al., 2011).

The analysis regarding the age at which accuracy and reaction time, demonstrated that it is at 57.49 years for the accuracy and 34.47 for the reaction time. The age effect found in the former is consistent with one of the biggest ageing studies, the Seattle longitudinal study (Hedden & Gabrieli, 2004), that showed an age effect from 60 years onwards. The same age was expected to have an effect on reaction time as well, but the age found instead, could reflect changes due to the decrease in the intelligence. As Horn and Cattel (1967) reported, fluid intelligence peaks in adolescence and then at around 30 or 40 years of age starts to decline. Since working memory (Oberauer et al, 2000; Oberauer et al., 2003; Salthouse, 1995; Salthouse, Babcock & Shaw, 1991 in Conway, 2005; Conway et al., 2003) and n back tasks (Gevins & Smith, 2000; Hockey & Geffen, 2004) are correlated with fluid intelligence this result could represent exactly this. In addition, this result is similar to what Germine, Duchaine & Hakayama (2011) found in the one study related to development and ageing regarding face recognition; in the short term memory task the age of decline in performance was present at 30 years. This early decline is supported also by neurobiological data: already at 20 years old people start to show reduced regional volume (Allen, et al., 2005; Fotenos, et al., 2005; Kruggel, 2006; Pieperhoff, et al., 2008; Sowell, et al., 2003 in Salthouse, 2009), reduced cortical thickness (Magnotta, et al., 1999; Salat, et al., 2004 in Salthouse, 2009), decrease in myelinisation (Hsu, Leemans, et al., 2008; Sullivan & Pfefferbaum, 2006 in Salthouse, 2009), changes in the receptor of serotonin (Sheline, et al., 2002 in Salthouse, 2009) and in striatal dopamine (Erixon-Lindroth, et al., 2005; Volkow, et al., 2000 in Salthouse, 2009). At the same age, more neurofibrillary tangle and metabolite in the brain also starts to become present (Del Tredici & Braak, 2008; Kadota, et al., 2001 in Salthouse, 2009).

Regarding the cognitive reserve results, accuracy and reaction time provided different results. As for the total score, the reaction time showed no effect on them. The difference in cognitive reserve is not related to a faster reaction time in a visuo-spatial working memory task, while accuracy showed an effect on it and an effect of it and age together; but those effects were independent of each other. This result could be caused by the fact that the effect of them are different: while increasing age causes a decrease in accuracies, an increase in the cognitive reserve score is related to an increase in accuracy as well. In the cognitive reserve regarding one's job, no effect of it was found in both accuracy and reaction time.

Differently, the cognitive reserve due to educational level had an effect on both. Relatively to the accuracy age and cognitive educational reserve, both had effects on accuracies but they were independent of each other. In the reaction time results, there was no effect of age, but an effect of condition as well as interaction between them. The cognitive reserve due to leisure time is not related to any difference in accuracy response, while it explains the reaction time as well as age does. No correlation between age and cognitive reserve due to leisure time was found; this could be due to the fact that while age decreases accuracy, cognitive reserve increases it. In addition, an interaction between the conditions and cognitive reserve due to leisure time was found.

Cognitive functioning, investigated by MMSE, showed an effect on both accuracy and reaction times and in both it had an effect deriving from age. Those two were independent of each other in both behavioural results. Nevertheless, one limit is that the younger participants had a ceiling effect and those participants were also the ones that totalized a better reaction time result in the task, especially in the higher load condition.

Finally, the gender effect was found only in the reaction time. As expected (Hampson & Kimura, 1992; Linn and Petersen 1985; Maccoby & Jacklin 1974; Voyer et al. 1995 in Moffat, Hampson & Hatzipantelis, 1998), males were faster than females.

To summarize, a visuo-spatial working memory task replicated the effects found in the verbal one. Taking into account a bigger range of ages, it was possible to see that accuracy starts to decrease at a later time and those results showed that reaction times are more sensible to the effect related to the cognitive reserve and due to the effect of gender. In conclusion, ageing affects working memory in different ways working memory with an earlier effect on reaction times. Cognitive reserve due to educational level as well as leisure time have a positive effect on the working memory task.

To conclude, healthy ageing affects visuo-spatial working memory, but cognitive reserve can have a positive effect on it.

CHAPTER 3

Behavioural, electrophysiological and hemodynamic correlates of visuo-spatial working memory in different ages. Within and between comparisons in adult and elderly participants during an n back task.

3.1 Introduction

As detailed in the previous chapters, working memory is a function negatively affected by ageing (Bopp & Verhaeghen 2005; Salthouse & Babcock 1991; Salthouse 1996 in Missonnier et al. 2004).

This is detectable in different correlates measured by previous studies.

Regarding the behavioural correlates, most of the works reported a decrease in accuracy due to age. In three of them this pattern was present for both control and experimental conditions (Vaughan et al, 2008; Van Gerven, 2008; Daffner et al., 2011), suggesting a general increase in errors due to age, independent of the working memory itself. While, other papers, showed a decrement in accuracy caused by aging only in experimental conditions (Voelcher-Rehage, Stronger and Alberts, 2006; Vermeji et al., 2012). In those works, the control condition shows no differences between adult and old-age participants. Finally, other authors found this effect only in the higher cognitive load condition, such as 2 and 3 back (Gajewski and Falkenstein, 2014; Mattay et al., 2006). The same was true in Wild-Wall, Falkenstein and Gajewski's work (2011), but no comparison with other conditions was made, since they used only 2 back task.

The reaction time, as well, shows an influence due to age. In some studies, age caused an increment in the reaction time in both control and working memory tasks with different cognitive loads (Mattay et al., 2006; Missioner et al., 2004; Vaughan et al, 2008; Van Gerven, 2008; Gajewski and Falkestein, 2014). Differently, Daffner et al. (2011) found an age effect only in the 2 back and no effect in the 0 condition. In addition, Wild-Wall, Falkenstein and Gajewski (2011) found an effect due to age in the 2 back, which was the only condition used. Only one study, Vermeji et al. (2012) did not find any differences between groups due to age.

All of those studies used letters or numbers as stimuli.

The same pattern was found in only one study that carried out a visuo-spatial task (Schmiedek, Li & Lindenberger, 2009).

Differences in anatomical correlates due to age were found. Nyberg et al. (2009) using fMRI showing that increasing the number of items to remember caused more activation in the left prefrontal cortex and left thalamus in adult participants and an opposite pattern in the elderly. Mattay and colleagues (2006) showed the same, but with a bilateral, prefrontal pattern. Due to age, a compensation mechanism was also detectable in the prefrontal cortex, but it is efficient only with a smaller amount of information to retain. The age effect in the cognitive load can be represented as an inverted U function (Mattay et al., 2006). With another technique, fNIRS, Vermeji et al. (2012) had coherent results: younger participants activated the left prefrontal cortex in an n back letters task, while for the elderly it was both left and right. Only two channels were used in this work (one on the right and one on the left part of the prefrontal area).

Similar to neuroanatomical and behavioural correlates, also the psychophysiological ones showed ageing effects. The components that showed an aging effect were P2, P3 and N3.

The first one, P2, is a positive peak normally found around 200 milliseconds after the stimulus onset. It shows the attentional process.

Regarding the latency, in some studies the peak comes later due to age (Goodin et al., 1978; Picton et al., 1984; Goodin and Aminoff, 1986; Hoemberg et al., 1986; Iragui et al., 1993 in Anderson et al., 1996; Anderson et al., 1996) while in others no changes were found (Brown et al., 1983; Pfefferbaum et al., 1984; Barrett et al., 1987 in Anderson et al., 1996). Anderson et al. (1996) found an effect of age and latency in the scalp: in the young participants, the latency peak was later in the parietal electrodes, compared to the frontal ones, while in the elderly participants the pattern was reversed. Regarding the amplitude, the component decreases with age (Anderson et al, 1996). Coherent with literature that did not find any differences, Finningan et al. (2011) supported this result regarding the latency in the prefrontal channels. Regarding the amplitude, it was bigger in the parietal site of younger participants (Finningan, 2011).

P3 was the most studied component with regards to this topic. This component is formed by two different waves, called P3a and P3b. The P3a, normally visible at Cz, is related to attention being driven to the stimulus and to the voluntary aspect of the novelty perception (Daffner et al., 2005; Falkenstein et al., 1994; Friedman et al., 2001; in Gajewsky and Falkenstein, 2014; Polich, 2007). The P3b, present at Pz, is related to memory processing and the allocation of cognitive resources (Polich, 2007).

Most of the studies found no effect on the latency due to age (Frtusova, Phillips and Winneke, 2013; Friedman, Simpson, & Hamberger, 1993; Vesco, Bone, Ryan, & Polich, 1993; Walhovd, Rosquist, & Fjell, 2008 in Frtusova, Phillips and Winneke, 2013), while Gajewsky and Falkenstein (2014) and Daffner et al. (2011) found a later peak in elderly participants. Regarding the amplitude, Gajewsky and Falkenstein (2014) found an increase in amplitude of both the P3a at Cz and the P3b at Pz. The reduction in the P3a could be read as uncertainty in the selection of the response in the older participants (Gajewsky and Falkenstein, 2014). The effect due to age in the P3b seems to be related to the selection of the response as well, linked to behavioural performance (Gajewsky and Falkenstein, 2014). Daffner et al. (2011) found a bigger amplitude in the P3 and it was found more anteriorly compared to the young participants. This can be explained as a compensation mechanism activated by the elderly, in which they recruited the anterior zone to perform the task (Daffner et al., 2011). Wild-Wall, Falkenstein and Gajewski (2011) found a smaller amplitude due to age and the elderly had less P3 in the parietal zone. This can underlie an ineffective maintenance of the stimulus (Wild-Wall, Falkenstein and Gajewski, 2011).

Finally, the N3 showed an age effect, and this seems to be related to the thinning of the anterior cingulate cortex. What is affected is not the latency, but the production of this type of response: in Daffner et al. (2011) the older participants did not show this component, while the younger ones did. The same result was found by West and Covell (2001), who linked this alteration to an impaired maintenance mechanism.

All of the studies performed until now collected behavioural and neuroanatomical or electrophysiological data, but not all of them at the same time, so this present study was carried out in order to fill this lack. One approach to having all of this data at the same time is to use a co-registration of EEG and fNIRS, as well as a collection of behavioural data.

Like fMRI, fNIRS is a technique based on the vascular coupling process; in this process, the active neurons required oxygenated blood. Several studies show that an increase in cerebral activity is related to an increase in bloodstream flow (Nielsen & Lauritzen, 2001; Chaigneau et al., 2007). Vascular coupling is affected by a reduction in cognitive performance (Jennings et al., 2005), hypertension (Fujishima et al., 1995), Alzheimer's disease even in the pre-clinical period (Iadecola, 2004), obesity (Tusek et al., 2014) and ageing, especially in elderly who hadn't practiced sports during their life. Two hypothesis explain this phenomenon: the first one is that in elderly participants the vascular system is dilated by default, the second one maintains that those who did not practice sports lost the capillary beds (Isaacs et al., 1992). One does not exclude the other.

The choice of using fNIRS in order to have the anatomical correlates is due to the characteristics of the technique itself. In particular, it gives oxygenate and deoxygenate data comparable to the fMRI technique, which is the gold standard of neuroanatomical tools. The oxygenated haemoglobin seems to be the one that correlates more with the blood-oxygen level dependent signal of fMRI. This is probably due to the good signal to noise ratio that the oxygenated haemoglobin of fNIRS has (Mehagnoul-Schipper et al. 2002; Kennan et al. 2002; Okamoto et al. 2004; Hoge et al. 2005; Toronov, Zhang & Webb

2007 in Kopton & Kenning 2014). Cui et al. (2011) published a work with the aim of investigating the similarity between those two tools in different cognitive tasks and they highlighted a good correlation with the BOLD signal and both oxygenated and deoxygenated haemoglobin; as previously mentioned, between the two, the oxygenate one has the best correlation. Another reason to use fNIRS is that the type of task, cognitive or motor, did not affect the correlation. The better signal came from the frontal and parietal zones; in those areas, there was a better signal to noise ratio, probably due to anatomical characteristics per se (Cui et al., 2011). Moreover, that study showed that both techniques give comparable results in an n back task. Nevertheless, fNIRS has some advantages compared to fMRI. The most important one is that it can be used in an ecological setting; the participants do not have to lie down in an enclosed box and they can move freely, since fNIRS tolerates this type of artefact (Plichta et al. 2011; Piper et al. 2014 in Kopton & Kenning 2014). Moreover, it costs less than the fMRI (Shimokawa et al. 2009 in Kopton & Kenning 2014) and it has a better temporal resolution: the frequency ranged from 3 to 100 Hertz (Kopton & Kenning 2014). fNIRS has disadvantages as well. It has less spatial resolution than fMRI (Kopton & Kenning, 2014), less signal to noise ratio and it can measure only the cortex hemodynamic response, since the data comes from the first 3 cm of the scalp.

Since the aim of this study was to study visuo-spatial working memory due to age with EEG and fNIRS, the n back paradigm used in the Cui et al. (2011) paper was used. This has several advantages. The first one is the data found can be compared with fMRI; the second one is related to the fact that in the literature only verbal tasks were previously used, so a gap remains regarding visuo-spatial ones. Finally, since visuo-spatial tasks is language-free, it is particularly suitable in research and in clinical settings.

Finally, in both groups participants with a high educational level and cognitive reserve were recruited (Daffner et al., 2011).

The hypothesis was to find, as previously found in the literature, a decrease in the behavioural data with a high cognitive load, as well as a decrement in attention and response selection (amplitude of P2 and latency of P3) and less maintenance (amplitude of N3) due to age. Regarding the hemodynamic response, more activation in the low cognitive load was expected as well as less activation during high cognitive ones in the prefrontal cortex. fNIRS covered only the prefrontal zone, due to its involvement in working memory (D'Esposito et al., 1998; Smith and Jonides, 1999; Owen et al., 2005; Takeuchi et al., 2012) and due to its suitability for this type of data (Cui et al., 2011; Masataka, Perlovsky & Hiraki, 2015). The novelty of this study also consists in finding what behavioural, hemodynamic and electrophysiological correlates of age have in common, in order to have better knowledge about this phenomenon and a specific explanation of it.

In addition, the effect within groups was taken into account. In particular, the expectation was to find slower reaction times (Luu et al. 2014; Chen, Mitra & Schlaghecken 2008; Watter, Geffen & Geffen 2001; Chen e Mitra 2009; Bomba e Singhal 2010; Rämä et al. 2000) and less accuracy (Chen, Mitra & Schlaghecken 2008; Watter, Geffen & Geffen 2001; Chen e Mitra 2009; Bomba e Singhal 2010; Rämä et al. 2000) as working memory load increased.

Regarding the neuro-anatomical results, previous works showed lateralized activation during visuo-spatial tasks: participants activate the right hemisphere more than the left (Molteni, 2009; Vermeji et al. 2012). Moreover, when the cognitive load increased, both oxygenated and deoxygenated haemoglobin increased in the prefrontal cortex (Herff et al., 2014; Molteni, 2009; Vermeji et al., 2012; Leon-Dominguez, Martin-Rodriguez & Leon-Carrion, 2015). The areas that seemed to respond selectively to the cognitive load were the dorsolateral prefrontal cortex (Molteni, 2009) as well as the lateral frontal pole, paracingulate gyrus, inferior, middle and superior frontal gyri and occipital and parietal posterior regions (Van Evijk et al., 2015). In addition, the precentral gyrus in the primary motor cortex and premotor cortex were also active due to the responses required during the task (Dores et al., 2015) as well as the right inferior parietal cortex, which seems to be the store of the visuo-spatial information in Baddeley's working memory model (Dores et al., 2015). The premotor cortex as well as the lateral frontal pole and middle and superior frontal gyri are expected to be more active at the increase in working memory load. Moreover, a right lateralized response is expected.

Concerning the psychophysiological correlates, the P2 was expected to present less amplitude with the increase in working memory load (Finningan et al, 2011) and to have more latency in the stimulus related to the task (Chen & Mitra, 2009). In the P3 it was expected that there would be an increment in latency due to the difficulty of the task, as shown in the work of Watter et al. (2001); in Chen and Mitra's one (2009) the latency decrement when task difficulty increased. Regarding the amplitude, a bigger one for the target stimulus was hypothesized as well as a bigger one in the parietal electrode than in the central and prefrontal ones (Watter et al., 2001).

3.2 Method

3.2.1 Participants

The participants were 17 aged between 20 and 30 years old in the young group and 16 aged between 60 and 70 in the older one. In the young group 9 were males and 8 females and in the older group the number of males and females was the same.

Inclusion criteria were: self-reporting of healthy status and normal or correct-to-normal vision. Exclusion criteria were: history of neurological disorders, psychiatric illness, report of depression or anxiety, use of psychotropic medications, a score in MMSE below 24 (Folstein, Folstein, & McHugh, 1975), a score in ANT below 14 (Sager, Hermann, LaRue & Woodard, 2006) and a score in the Beck depression inventory 2 (BDI-II) above 14 (Beck, 1967). Some pathologies were also considered as exclusion criteria due to the possible confound in the hemodynamic, behavioural and electrophysiological data. Those were diabetes, hypertension, coronary disease, vasculopathy, stroke, apnea-hypopnea syndrome, pneumopathy, obstructive pulmonary disease, cirrhosis of the liver, hepatitis C, renal impairment, hypothyroidism and hyperthyroidism.

All the participants met the inclusion criteria. The two groups did not differ in their educational level (M young=19.02, ds=2.22; M old=15.71, ds=4.19) [$t(18.897)=1.507$, $p=.304$] nor in their ANT results (M young=26.87, ds=6.83; M old=24.5, ds=7.26) [$t(26.931)=.919$, $p=.366$] nor the cognitive reserve due to the educational level (M young=120.81 ds=15.77; M old=131.71 ds=25.78) [$t(20.960)=-1.373$, $p=.184$]. The MMSE results was lower in the old participants (M young=29.82, ds=.39; M old=28.36, ds=1.9) [$t(13.917)=2.823$, $p=.014$], but still in the normal range. On the other hand, the cognitive reserve due to job as well as leisure time and total score were higher in the older group (M cri-total=130.57 ds=20.27; M cri-job=124.14 ds=14; M leisure time=120.71 ds=18.06) than the younger ones (M cri-total=107.6 ds=11.96; M cri-job=93.81 ds=8.6; M leisure time=96.18 ds=5.07) [$t(20.485)=-3.797$, $p=.001$] [$t(21.081)=-7.026$, $p=.000$] [$t(14.797)=-4.914$, $p=.000$]. The part of the Cri-q test in which are calculated these cognitive reserves, is based on how long, in years, one action is done. Therefore, since the old participants per se had more years to perform one action, this seems to be the explanation for the found results.

3.2.2 Task and tests

The task and the tests were the same used in the previous study (more details are reported in 2.2.2 paragraph).

In this study there was a questionnaire more. The BDI-II is a self-administered questionnaire which investigates the depression level (The test is reported in the appendix). It is formed of 21 items. Each item is formed of one or more reply referred to symptoms and for each of them the participants had to choice which one better described how they felt in the previous two weeks.

The behavioural, electrophysiological and haemodynamic data were collected at the same time during the task administration.

The behavioural data, accuracy and reaction time, were collected by E-prime software (Psychology Software Tools, Pittsburgh, PA).

A thirty-two channels Acticap, with the Brain Quick system of Micromed (Micromed, Brain Quick system 98, Treviso, Italy), recorded the electrophysiological data. The electrodes were arranged on the scalp was based on 10-20 international systems of electrodes placement. The channels were positioned in AFp1, AFp2, F7, AFF5h, FCz, AFF6h, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2, FC5, FC1, FC2, FC6, CP5, POz, CP1, CP2, CP6, PO3 e PO4 (Figure 24a). The on-line reference was at Fcz. The impedance was kept below 5 kΩ. Moreover, two bipolar electrodes recorded ocular movements (both horizontal and vertical).

The haemodynamic data (oxygenated and deoxygenated haemoglobin) were recorded by 20 channel of the NIRScout machine, continuous wave one one (NIRx Medical Technologies LLC). The optodes were positioned in the prefrontal area. The channels arrange in the scalp was based on 10-20 international system. The 8 sources were positioned at Fpz, AF7, AF8, AF3, AF4, Fz, F3, F4 and the 7 detectors at Fp1, Fp2, Afz, F1, F2, F5 e F6 (Figure 24b). The optodes were positioned in the same cap as the EEG electrodes and before the beginning of the registration, a calibration was carried out by NIRStar 14 (NIRx Medical Technologies LLC), in order to have a good enough signal or a good gain, or both.

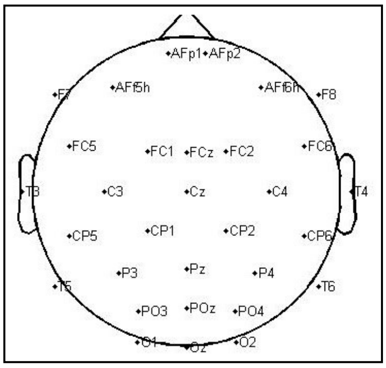


Figure 24a The EEG montage. The electrodes with them labels are shown as they are placed in the participant's scalp. The left and right part correspond to the left and right hemisphere, respectively.

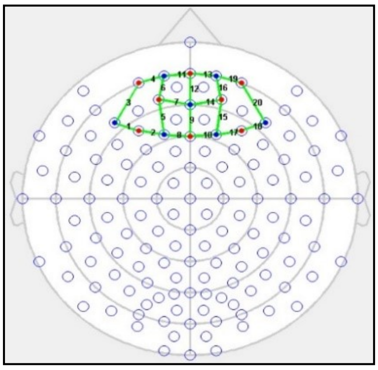


Figure 24b The fNIRS montage. The red dots represent the emitters and the blue ones the detectors. The light green lines represent the channels. The left and right part correspond to the left and right hemisphere, respectively.

3.2.3 Procedure

All the participants were tested in the afternoon. They arrived at the laboratory and firstly, they signed the informed consensus form, albeit they were unaware of the aim of the study.

Initially the cap was put on the head of the participant and then the EEG electrodes were placed. Secondly, the fNIRS optodes were placed and after that the task started.

At the end of the task there were the tests (MMSE, ANT, CRI-q, BDI-II) and questions about health status of the participants were administered.

3.2.4 Data analysis

Regarding the behavioural data, both accuracies and reaction times were analysed. The three different conditions (control, low and high cognitive load) were compared to each other both within and between groups. In the within analysis three t-tests were carried out and the results were corrected with Bonferroni correction for multiple comparison. Regarding the between analysis each condition was compared between the two groups. All the analysis were carried out with SPSS software (IBM SPSS, version 22).

The electrophysiological analysis was formed of two parts. The first one, related to the pre-processing analysis, was carried out by Eeglab (version 13.4.4b) (Delome & Makeig, 2004) using Matlab software (version 2014a). The data was first filtered with a high pass filter at 30 hertz; secondly, a low pass filter at 0.1 hertz was used. A notch filter between 49 and 51 hertz was carried out as well, in order to exclude any network artefacts. The epochs were extracted from 200 to 1500 milliseconds before and after the stimulus, respectively and the baseline was computed between 200 milliseconds and the onset of the event. Successively, the eyes movements and muscular artefacts were excluded from the EEG data by the Independent Component Analysis (Delome & Makeig, 2004). The last step of the pre-processing consisted in removing the epochs that exceeded 100 μV and re-referencing the data by average reference. The second part, relating to the statistical analysis, was carried out with the Mass Univariate ERP Toolbox (Groppe, Urbach & Kutas, 2011) using Matlab software (version 2010b). Mass univariate analysis is a data driven analysis of the amplitude of the components. It is widely used in fMRI data analysis, due to its nature. This type of analysis has the advantage that it reduces a priori selection of the data (in terms of electrodes and time windows). Other benefits were the possible findings of unexpected effects as well as taking advantage of both spatial and temporal resolution of the EEG signal. The mass univariate analysis is based on a series of t-tests applied simultaneously to all the electrodes taking into account in a determined time window all the possible permutations between them; for each permutation a t score was calculated automatically. In order to avoid false positive results, false discovery rate correction (Benjamini & Yekutieli, 2001) was applied; it assess the level of significance using a level of 5% and it makes sure that the false discovery rate will be equal to or less than the 5% level, independently of the type and structure of the data (Benjamini & Yekutieli, 2001).

Regarding the time window, in order to be conservative, the same was selected in all comparisons. The beginning and the end was decided by a visual inspection and the window selected took into account all the visible changes. Within and between groups the same comparisons were carried out. The first comparison was between the cognitive load conditions: control, low and high were compared to each other in the time window comprising between 130 and 530 milliseconds from the onset of the stimulus. The other analysis compared the target and non target conditions, both within and between groups; the time point taken into account was between 130 and 730 milliseconds from the onset of the stimulus.

Since this analysis can take into account only the amplitude of the components, a series of general linear models were carried out in the latencies of the components found. These comparisons were used to detect possible differences both within and between the groups.

Finally, both the latencies and the amplitude of the components found were correlated by Pearson analysis against behavioural data (reaction time and accuracy).

The analysis of the haemodynamic data were carried out on both oxygenated and deoxygenated haemoglobin. They had, respectively, 760 and 850 nm wavelengths with 7.8125 hz of sampling rate. The analysis was carried out using NirsLab toolbox (201605 version). Initially, a pass-band filter between 0.01 and 0.2 hertz was applied. The selection of the filter is based on the frequency of the artefacts, such as breathing (between 0.16 and 0.35 hz with 10-20 breath per minute) and heart rate (0.6 hz with 40 beats per minute; 1.6 hz with 100 beats per minute). Mayer waves are changes in arterial blood pressure caused by oscillation in the baroreceptor and the chemoreceptor that reflect control system; they have a frequency of around 0.1 hz. Mayer waves and a part of the breathing artefact remained in the data after filtering at 0.01 and 0.2; this is a compromise in order to not lose other important information. In order to obtain the haemoglobin concentration the Lamber-Beer modified law was used (Lloyed et al., 2010); it allows a calculation of the relative concentration as a function of total photon path length. The Lamber-Beer modified low takes into account the attenuation coefficient that it is due to both the scattering and absorbed signal by the scalp. During the light passages going from the source to the detector, called banana shape, the light is in part absorbed by tissues and in part scattered (Figure 25)

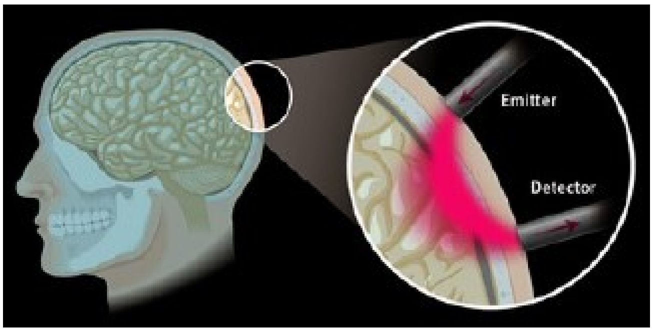


Figure 25 One emitter and one detector as well as the scattered light; as shown it has a banana shape.

The modified Lamber-Beer law (Figure 26) takes into account the differential path length factor. Since it changes due to age, the data was corrected based on the previous studies; there was no correction for the 60-70 years old group, so the closest value found in the literature was used (Duncan et al., 1996).

$$\Delta A = \varepsilon \cdot \Delta C \cdot L \cdot DFC$$

Figure 26 The Lamber-Beer modified law.

ΔA is the variation in the luminosity attenuation; it is the difference between the attenuation value in a determine instant (ration between the light emitted and the light received) compared to the reference one.

Ɛ is the molar extraction coefficient, which indicates the attenuation due to the absorption

ΔC is the variation in the concentration of the chromophore

L is the distance between emitter and detector (3 cm in this case)

DFC (differential path length factor) it is a coefficient based on scattering influence on photons phat. This value depend on age, sex and cerebral zone of the channel. It is not possible to calculate this value with continuous wave machine.

Regarding the oxygenated haemoglobin, 6.196 and 6.903 were used for the young and old respectively. In the deoxygenated haemoglobin data, 5.535 and 6.197 were respectively taken into account (Duncan et al., 1996). This value has an effect only in the between group comparisons. Finally, since NIRScout is a continuous wave machine, the values found are not absolute, but are a variation compared to zero, established in the 5 seconds that preceded the beginning of the block. The data collected with this tool is related to the entire block and not, as with the components of the EEG, to the events. It is possible to obtain event related data from the fNIRS data collection, but in this study a block design was used. This choice was due to the fact that, for obtaining good evoked potential results, at least 40 trials are needed and for good event related fNIRS data, 20 seconds are needed. Due to the nature of the signal per se (Ferrari & Quaresima 2012), it would have been too long a task. Moreover, a block design paradigm in fNIRS permits an average within the same conditions and this creates a better signal to noise ratio.

Regarding the statistical analysis of the haemodynamic data, a general linear model was applied by SPM analysis present in the Nirslab toolbox (Ye et al., 2009). This analysis is based on t test comparison between and within groups and it automatically gives a map with the statistically significant differences found.

In addition to this, correlations by Pearson analysis were carried out between the beta values found and the behavioural results. Moreover, the same comparisons were done with the evoked potential results with the aim of finding correlation between those two signals and to detect a possible arousal effect.

3.3 Results

3.3.1 Behavioural results

3.3.1.1 Within-group results

In the younger group, no differences were found in all of the comparison carried out in the accuracy: control condition and high and low cognitive load ones as well as high and cognitive load (Figure 27).

In the old participants the only comparison that showed an effect was the one between control (M=1 ds=.005) and high cognitive load conditions (M=0.91 ds=.110) [t(13)=3.045, p=.009] (Figure 28).

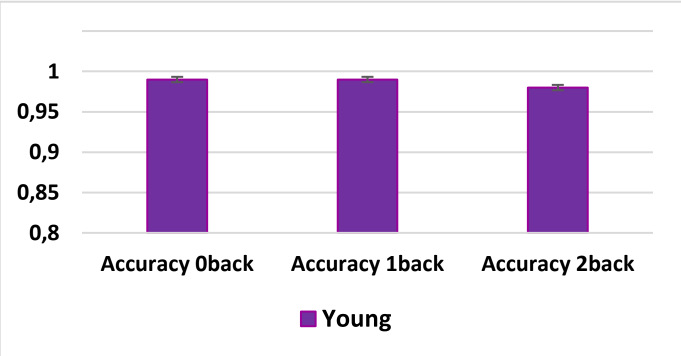


Figure 27 The accuracy under the different condition (different columns) in the young participants.

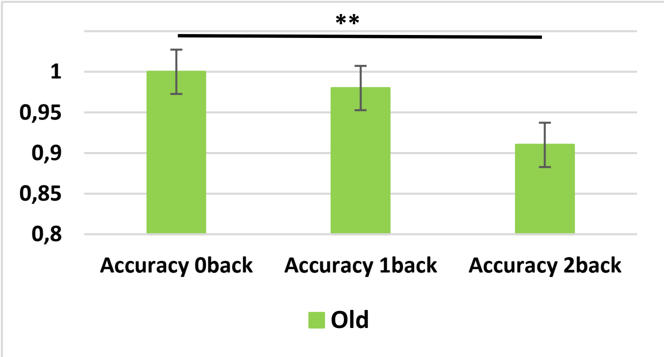


Figure 28 The accuracy under the different condition (different columns) in the old participants. The line and the asterisks indicates the statistical significant comparison, with a p value less than 0.01.

In the younger group, the reaction time under the highest cognitive load condition (M=414.12, ds=113.87) was slower than both control (M=329.44, ds=56.78) and low cognitive loads (M=337.82, ds=64.03) [t(16)=-4.684, p=.000] [t(16)=-3.721, p=.002]. In the 0 back participants were not faster in than the 1 back (Figure 29).

In the older participants group, all the comparisons showed effects of the memory load in the reaction times. The elderly in the high cognitive load (M=574.21, ds=127.14) were slower than both control condition (M=374.2, ds=58.27) [t(13)=-6.990, p=.000] and low cognitive one (M=412.36, ds=60.76) [t(13)=-6.326, p=.000]. Similarly, they were faster in the control condition (M=374.2, ds=58.27) than the low cognitive load one (M=412.36, ds=60.76) [t(13)=-5.006, p=.000] (Figure 30).

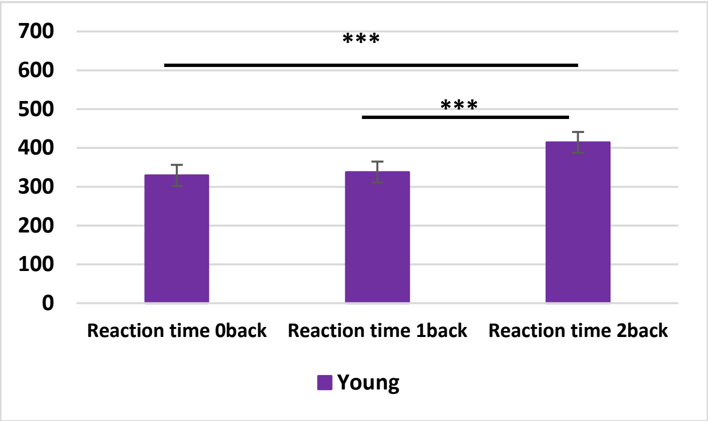


Figure 29 The reaction under the different condition (different columns) in the young participants. The line and the asterisks indicates the statistical significant comparison, with a p value less than 0.001.

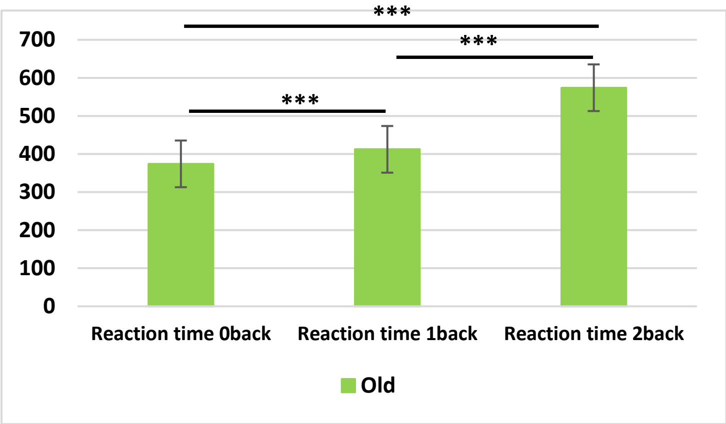


Figure 30 The accuracy under the different condition (different columns) in the old participants. The line and the asterisks indicates the statistical significant comparison, with a p value less than 0.001.

3.3.1.2 Between group results

The accuracies did not differ between the groups in both the control condition and the low cognitive load one. By comparison, in the higher cognitive load condition, the accuracies were higher in the younger (M=0.98, ds=0.045) participants than for the older ones (M=0.91, ds=0.110) [t(16.538)=2.296, p=.033](Figure 31).

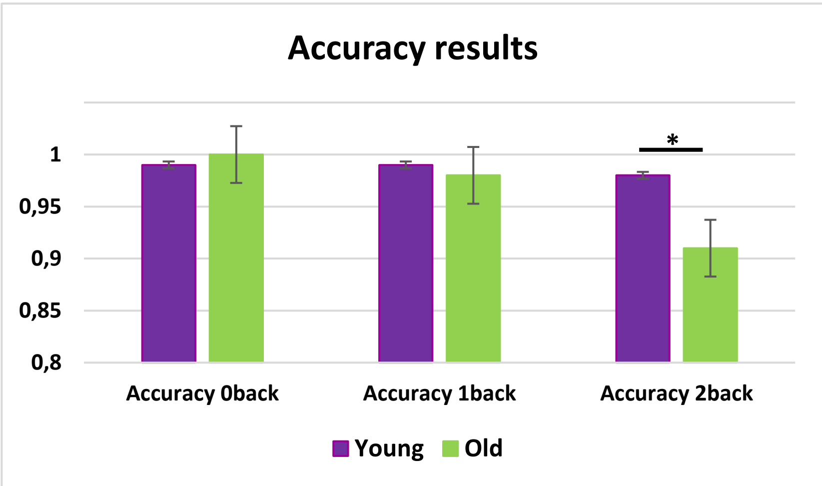


Figure 31 The accuracy under different condition (different columns) in the older (represented by the green colour) and the young (represent by the violet colour) participants. The line and the asterisk represent the statistical significance comparison, with a p value of 0.05.

All the conditions tested showed slower reaction times for the older participants. This pattern was found in the control condition (M old=374.2 ms, ds=58.27) (M young=329.44 ms , ds=56.78) [t(27.578)=-2.153, p=.040] as well as the low (M old=412.36, ds=60.76) (M young=337.82, ds=64.03) [t(28.371)=-3.317, p=.002] and high (M old=574.21 ds=127.14) (M young=414.12, ds=113.87) [t(26.465)=-3.656, p=.001] cognitive load ones (Figure 32).

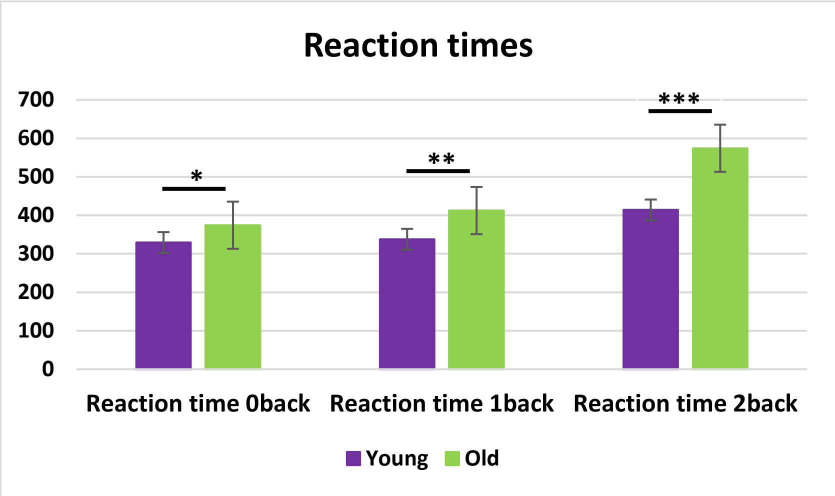


Figure 32 The reaction time under different conditions (different columns) for the older (represented by the green colour) and the young er (represent by the violet colour) participants. The line and the asterisk represent the statistical significance comparison. One asterisk represents a p value less than 0.05, two asterisks represent a p value less than 0.01 and three asterisks represent a p value less than 0.001.

3.3.2 Electrophysiological results

The analysis were carried out both within and between the groups. The conditions analysed were cognitive load: the control condition, low and high cognitive load were compared against each other. The comparison between the target and non target stimuli was carried out as well.

3.3.2.1 Condition results

3.3.2.1.1 Within groups results

For the younger participants in the high load condition (2 back), the P3 and the late positive component showed a higher amplitude than the control condition (0 back) (Figures 33, 34, 35).

Moreover, the P3 showed more latency under the high cognitive load condition (M=435.45, sd=68.79) than the control one at Pz (M=463.92, sd=74.17) [t(30)=-2.789, p=.007] (Figure 36). No difference in the LPC latency was found.

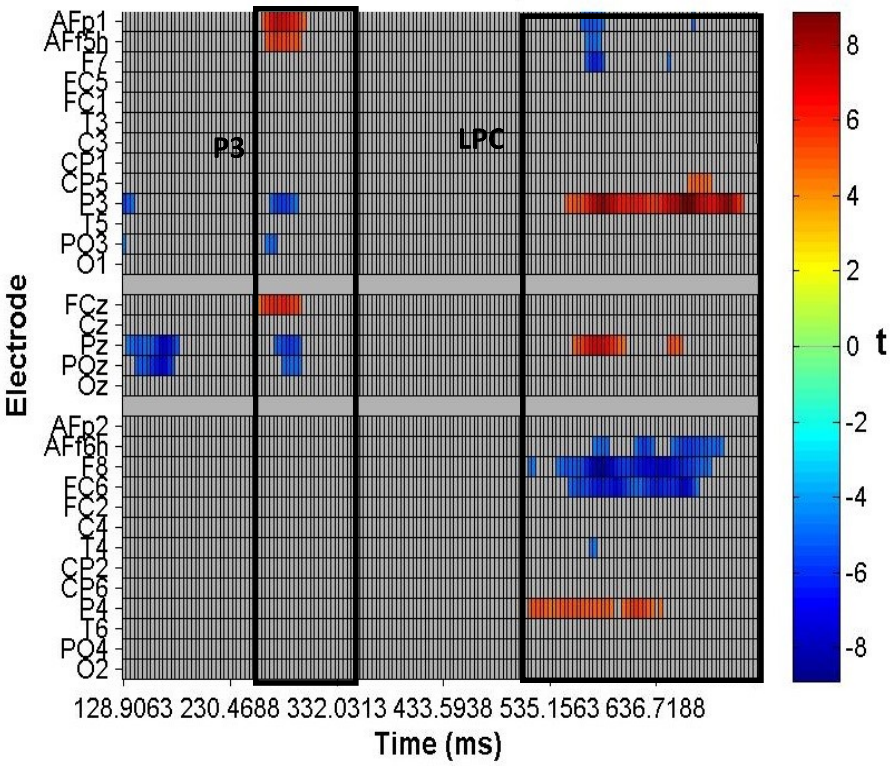


Figure 33 The evoked potential results. In the y-axis all the electrodes and in the x-axis the time points were shown. The coloured cells showed when and where the result is less than 0.5, after correction for multiple comparison. The red and blue colours represent the activation: the red one mean that the second item is less active than the first, while in the blue one the showed that the second item is more active than the first.

P3

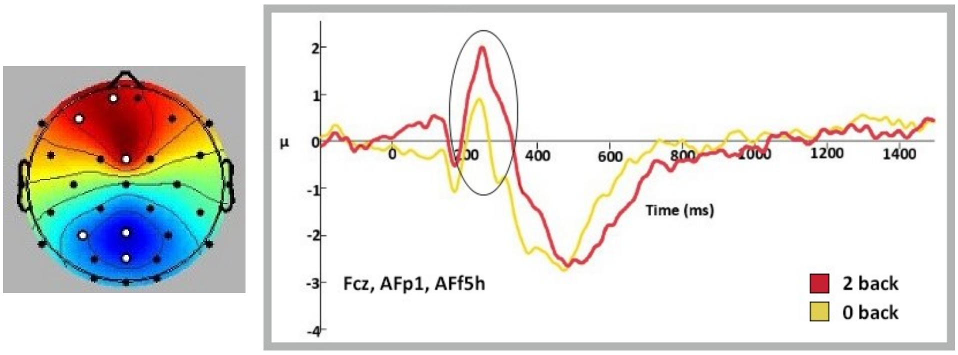


Figure 34 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white ones were. The red and blue colours represent the activation: the red one means that the second item is less active than the first, while in the blue one the second item is more active than the first.

The second figure shows the components found at Fcz, AFp1 and AFf5h in the high cognitive load and control condition. In the y-axis the amplitude (micron volt) is shown, while in the x-axis the time (milliseconds) is represented. The red line represent the high cognitive load condition and the yellow line the control one.

LPC

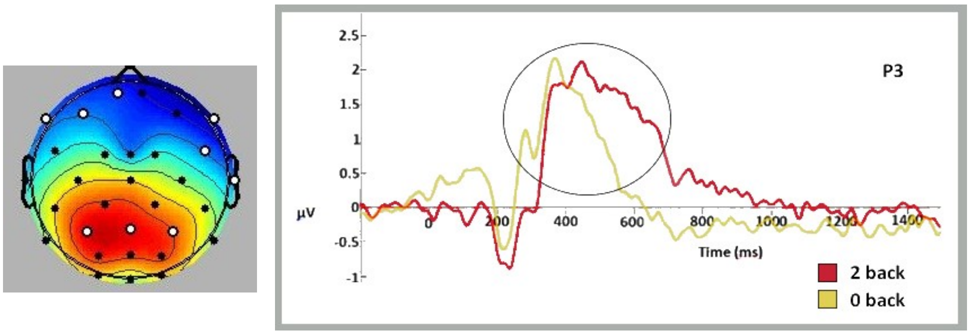


Figure 35 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white ones were. The red and blue colours represent the activation: the red one means that the second item is less active than the first, while in the blue one the second item is more active than the first.

The second figure shows the components found at Fcz, AFp1 and AFf5h in the high cognitive load and control condition. In the y-axis the amplitude (micron volt) is shown, while in the x-axis the time (milliseconds) is represented. The red line represent the high cognitive load condition and the yellow line the control one.

P3

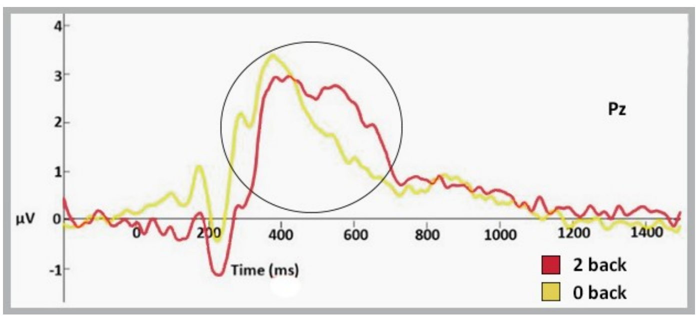


Figure 36 The difference in P3 latency at Pz electrode under the two conditions. On the y-axis the amplitude (micron volt) is shown, while in the x-axis the time (milliseconds) is represented. The red line represent the high cognitive load condition and the yellow line the control one.

Low cognitive load and high cognitive load condition showed differences as well. The P2 had a higher amplitude in the 2 back (Figures 37 and 38). Regarding the P3, the low cognitive load (1 back) showed higher amplitude than the high cognitive load condition (2 back) (Figures 37 and 39). No differences in the latency of both the components were found.

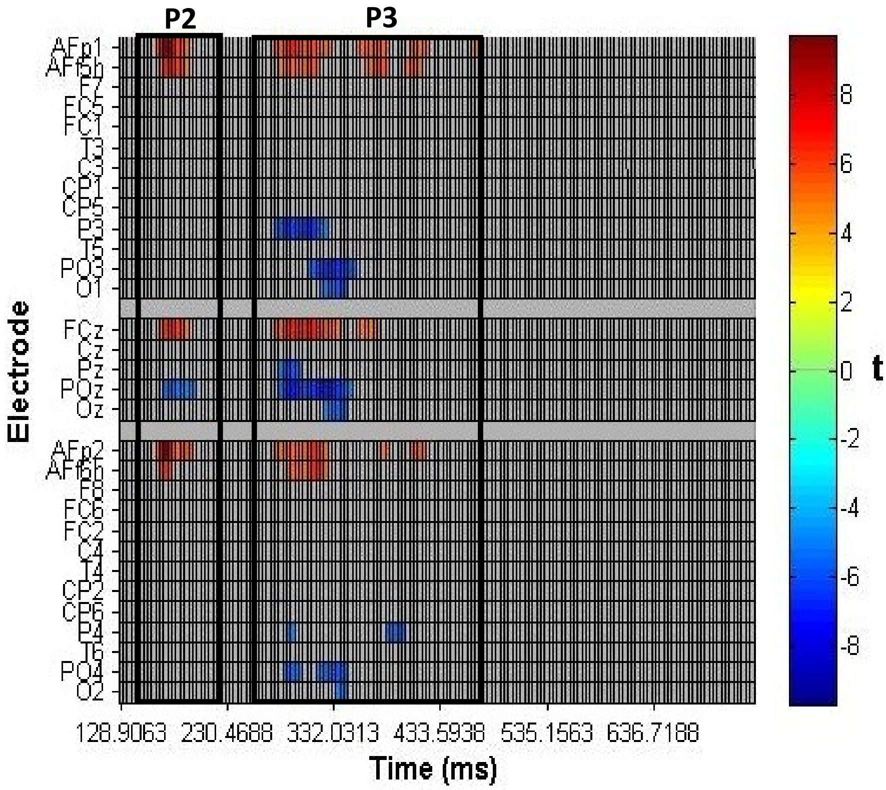


Figure 37 The evoked potential results. In the y-axis all the electrodes and in the x-axis the time points were shown. The coloured cells showed when and where the result is less than 0.5, after correction for multiple comparison. The red and blue colours represent the activation: the red one mean that the second item is less active than the first, while in the blue one the showed that the second item is more active than the first.

P2

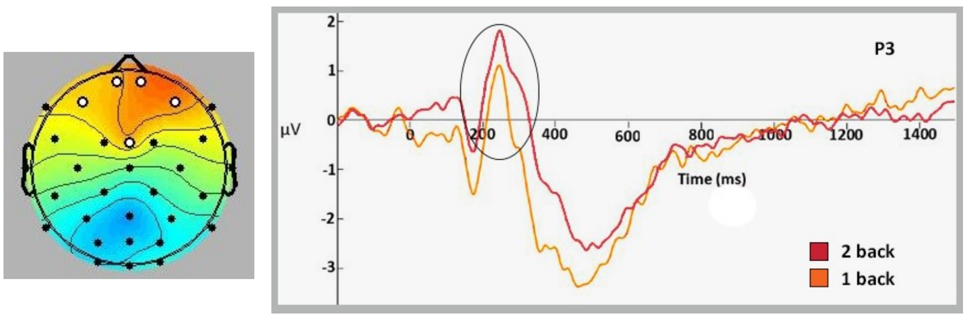


Figure 38 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white ones were. The red and blue colours represent the activation: the red one means that the second item is less active than the first, while in the blue one the second item is more active than the first.

The second figure shows the component found at the P3 electrode in the high and low cognitive load conditions. In the y-axis the amplitude (micron volt) is shown, while in the x-axis the time (milliseconds) is represented. The red line represent the high load condition and the yellow line the control one.

P3

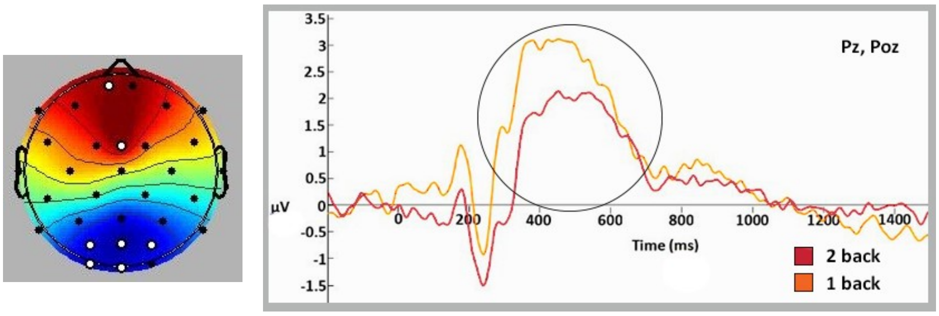


Figure 39 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white were. The red and blue colours represent the activation: the red one mean that the second item is less active than the first, while in the blue one the showed that the second item is more active than the first.

The second figure shows the component found at Pz and Poz electrodes in the high and low cognitive load conditions. In the y-axis the amplitude (micron volt) is shown, while in the x-axis the time (milliseconds) is represented. The red line represent the high cognitive load condition and the yellow line the control one.

No differences were found between the low cognitive load condition (1 back) and the control one (0 back).

In the older participants, no differences were found in all the comparisons carried out.

3.3.2.1.2 Between-groups results

In the highest cognitive load condition, no differences were found between the groups.

Regarding the low cognitive load one, the P2 had more amplitude for the older participants (Figures 40 and 41). No difference in latency was found.

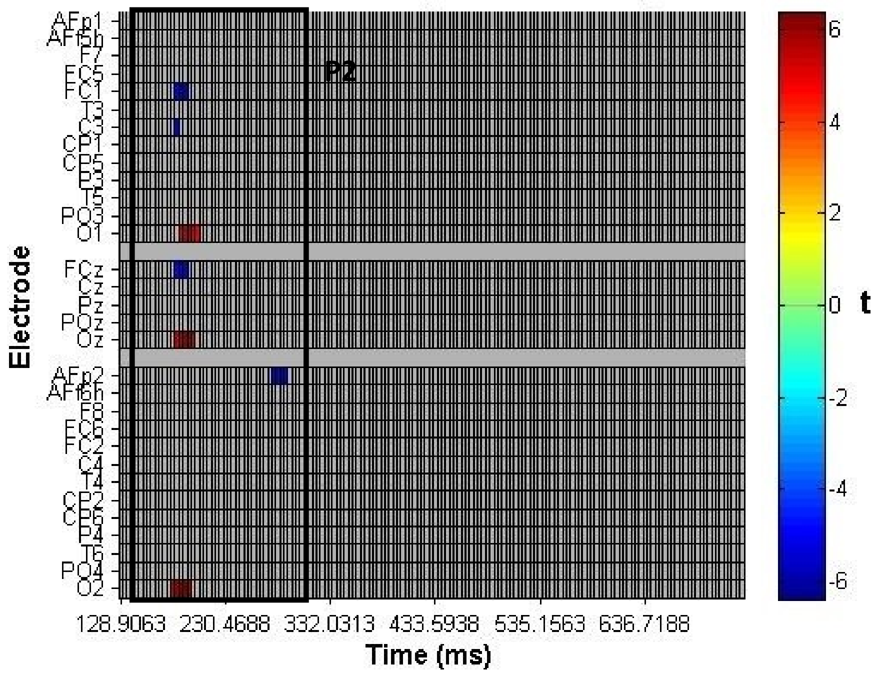


Figure 40 The evoked potential results. In the y-axis all the electrodes and in the x-axis the time points were shown. The coloured cells showed when and where the result is less than 0.5, after correction for multiple comparison. The red and blue colours represent the activation: the red one mean that the second item is less active than the first, while in the blue one the showed that the second item is more active than the first.

P2

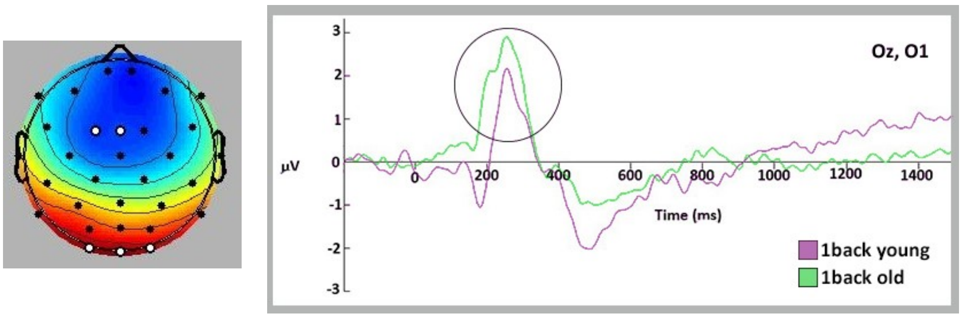


Figure 41 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white were. The red and blue colours represent the activation: the red one means that the second item is less active than the first, while in the blue one the second item is more active than the first.

The second figure shows the component found at the Oz and O1 electrodes in the low cognitive load condition in the two groups. In the y-axis the amplitude (micron volt) is shown, while in the x-axis the time (milliseconds) is represented. The violet line represent the young participants result, while the green line the elderly one.

The comparison between the control condition for the two groups showed significant differences. As in the 1 back condition comparison, the P2 showed a higher amplitude in the older group (Figures 42 and 43). The P3 showed an opposite pattern, with a bigger amplitude in the younger participants group (Figures 42 and 44). No differences in latencies were found.

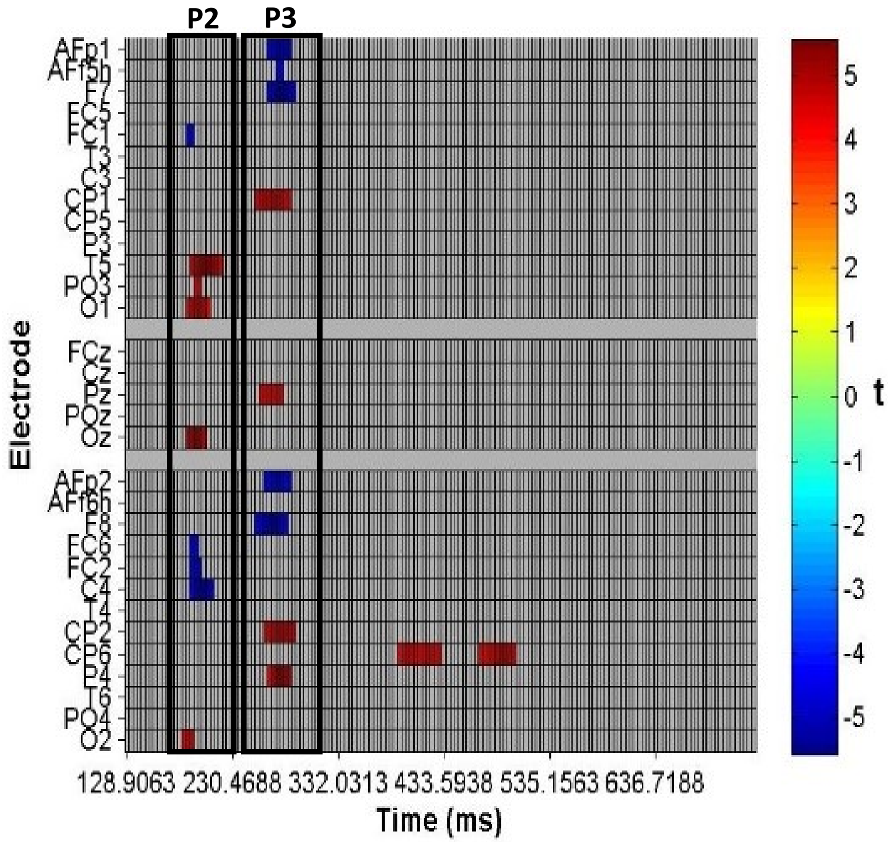


Figure 42 The evoked potential results. On the y-axis all the electrodes and on the x-axis the time points were shown. The coloured cells showed when and where the result is less than 0.5, after correction for multiple comparison. The red and blue colours represent the activation: the red one mean that the second item is less active than the first, while in the blue one the showed that the second item is more active than the first.

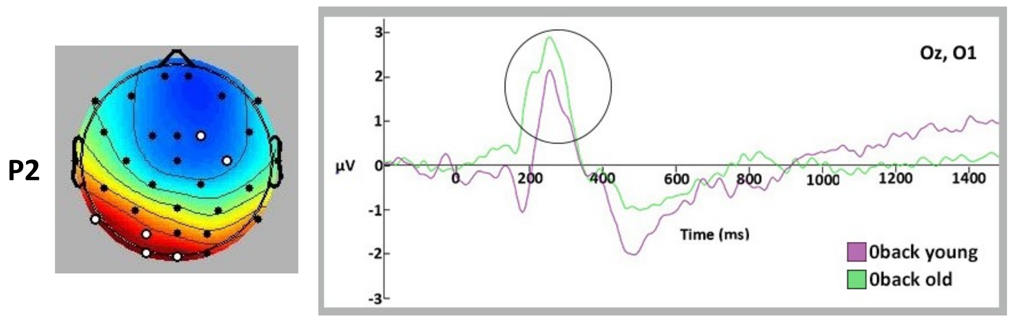


Figure 43 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white were. The red and blue colours represent the activation: the red one means that the second item is less active than the first, while in the blue one the second item is more active than the first.

The second figure shows the component found at the Oz and O1 electrodes in the control condition in the two groups. In the y-axis the amplitude (micron volt) is shown, while in the x-axis the time (milliseconds) is represented. The violet line represent the young group result, while the green line the elderly one.

P3

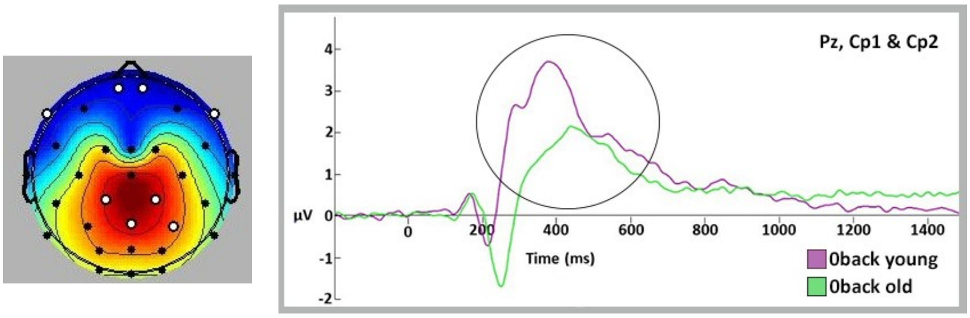


Figure 44 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white ones were. The red and blue colours represent the activation: the red one means that the second item is less active than the first, while in the blue one the second item is more active than the first.

The second figure shows the component found at the Pz, Cp1 and Cp2 electrodes in the control condition in the two groups. In the y-axis the amplitude (micron volt) is shown, while in the x-axis the time (milliseconds) is represented. The violet line represent the young group result, while the green line the elderly one.

3.3.2.2 Target and non target results

3.3.2.2.1 Within-group results

In the younger group, the P3 had a bigger amplitude in the target rather than the non target stimulus (Figures 45 and 46). No differences in latency were found.

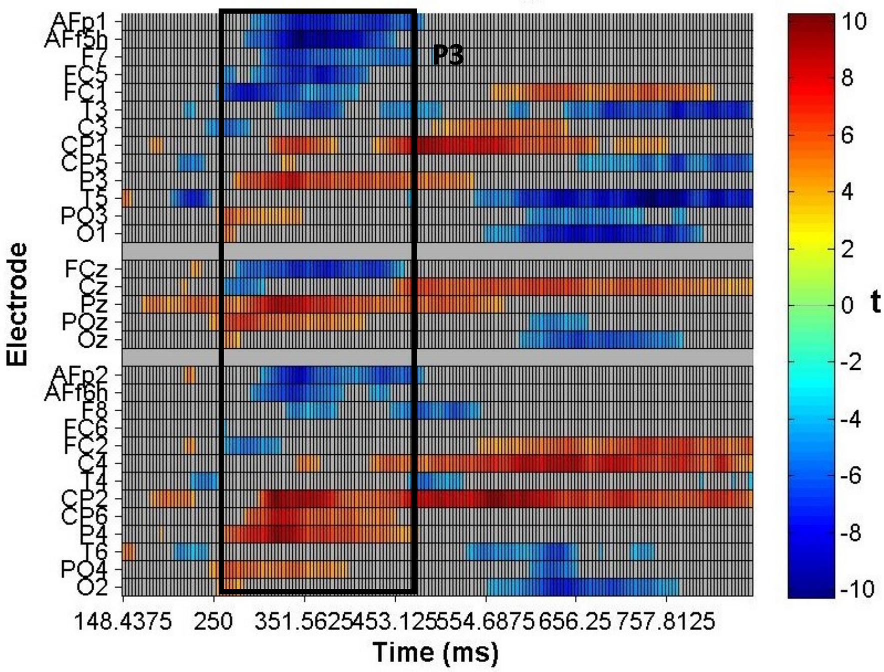


Figure 45 The evoked potential results. On the y-axis all the electrodes and on the x-axis the time points were shown. The coloured cells showed when and where the result is less than 0.5, after correction for multiple comparison. The red and blue colours represent the activation: the red one mean that the second item is less active than the first, while in the blue one the showed that the second item is more active than the first.

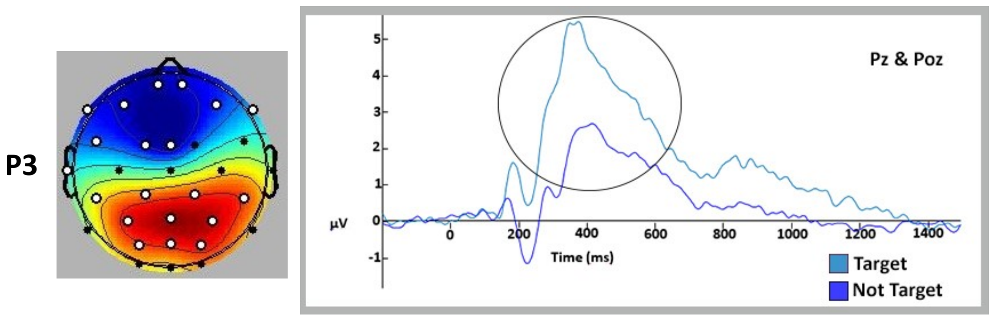


Figure 46 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white ones were. The red and blue colours represent the activation: the red one means that the second item is less active than the first, while in the blue one the second item is more active than the first.

The second figure shows the component found at Pz and Poz electrodes in the target and non target conditions in the younger group. On the y-axis the amplitude (micron volt) is shown, while on the x-axis the time (milliseconds) is represented. The light blue line represents the target, while the blue one the not target.

No differences were found between the two conditions in the elderly.

3.3.2.2.2 Between-group results

In the target condition, the adult participants had higher amplitude in the N3 component, in the frontal pole (Figures 47 and 48). Moreover, the P3 showed a later latency peak for the elderly (M=421.68, ds=90.46; M=489.42, ds=73.87) [t(28.486)=-2.289, p=.030] (Figure 49).

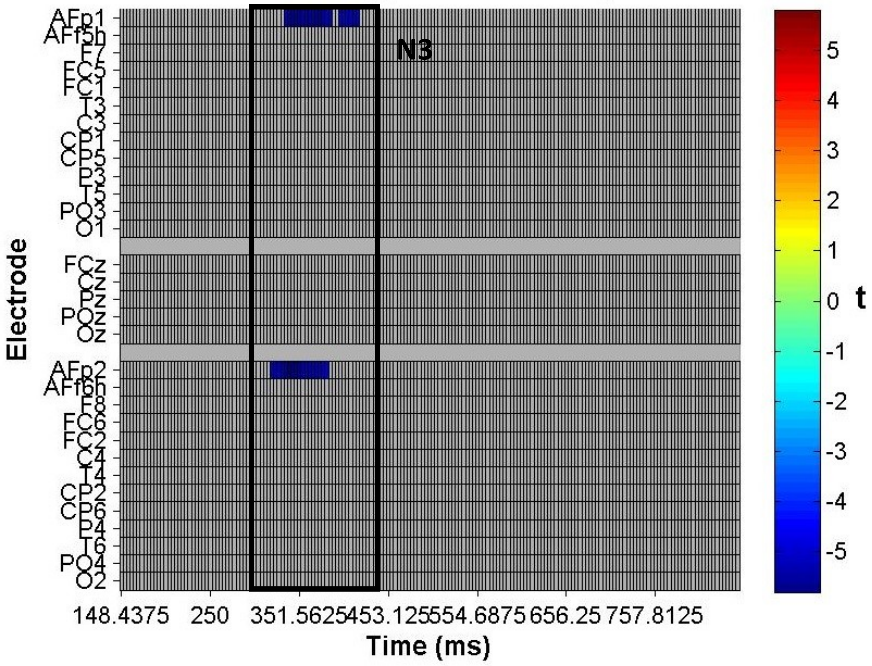


Figure 47 The evoked potential results. On the y-axis all the electrodes and on the x-axis the time points were shown. The coloured cells showed when and where the result is less than 0.5, after correction for multiple comparison. The red and blue colours represent the activation: the red one mean that the second item is less active than the first, while in the blue one the showed that the second item is more active than the first.

N3

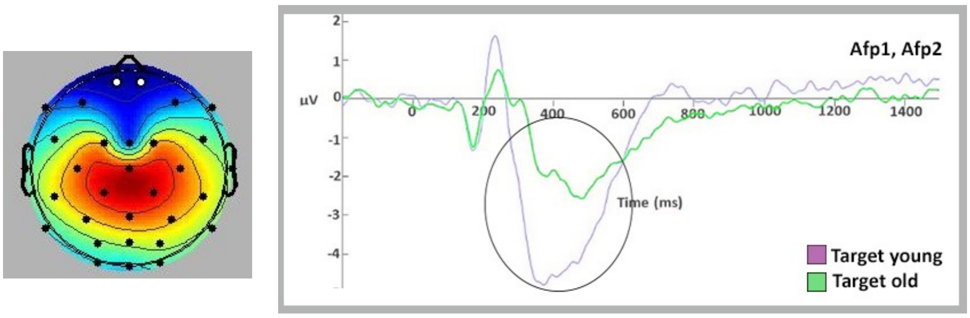


Figure 48 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white ones were. The blue colours represent the activation: the red one means that the second item is less active than the first, while in the blue one the second item is more active than the first.

The second figure shows the component found at Afp1 and Afp2 electrodes in the target condition in the young and old participants. On the y-axis the amplitude (micron volt) is shown, while on the x-axis the time (milliseconds) is represented. The light violet line represents the target condition in the young participants, while the blue the target condition in the elderly group.

P3

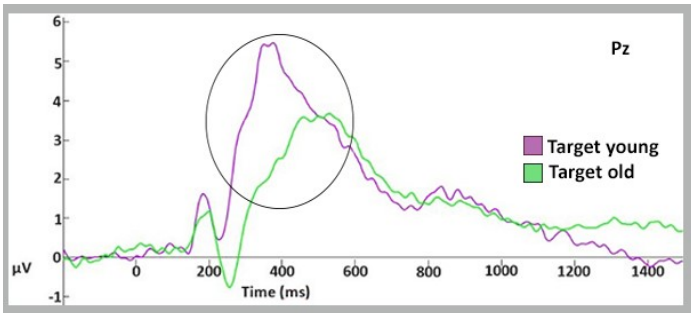


Figure 49 The difference in P3 latency at Pz electrode in the two groups. On the y-axis the (micron volt) is shown, while on the x-axis the time (milliseconds) is represented. The violet line represents the target condition in the young group, while the green one the same condition in the old group.

In the non target condition, the P2 (Figures 50 and 51) and P3 (Figures 50 and 52) had higher amplitudes in the younger adult participants. No differences in the latency of P2 and P3 were found.

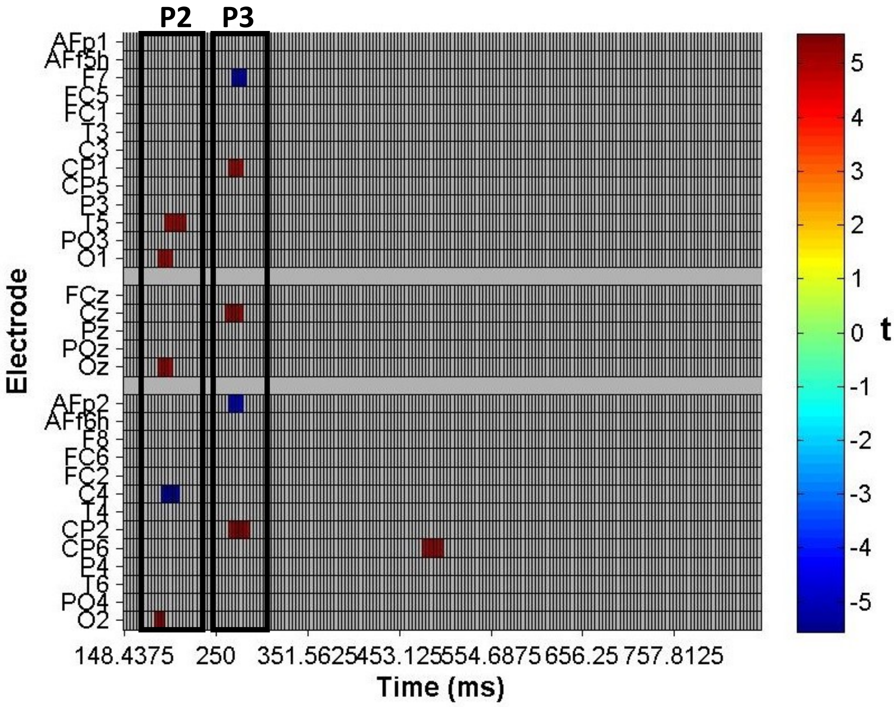


Figure 50 The evoked potential results. On the y-axis all the electrodes and on the x-axis the time points were shown. The coloured cells showed when and where the result is less than 0.5, after correction for multiple comparison. The red and blue colours represent the activation: the red one mean that the second item is less active than the first, while in the blue one the showed that the second item is more active than the first.

P2

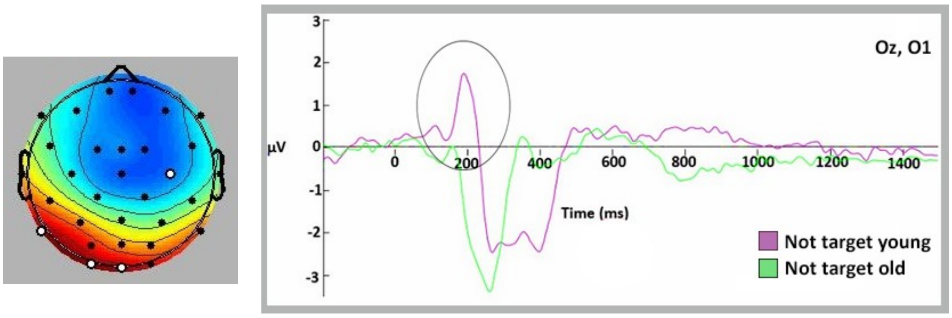


Figure 51 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white ones were. The red and blue colours represent the activation: the red one means that the second item is less active than the first, while in the blue one the second item is more active than the first.

The second figure shows the component found at Oz and O1 electrodes in the non target condition in the younger and old groups. On the y-axis the amplitude (micron volt) is shown, while on the x-axis the time (milliseconds) is represented. The light violet line represents the not target condition in the young group, while the green line the not target condition in the old one.

P3

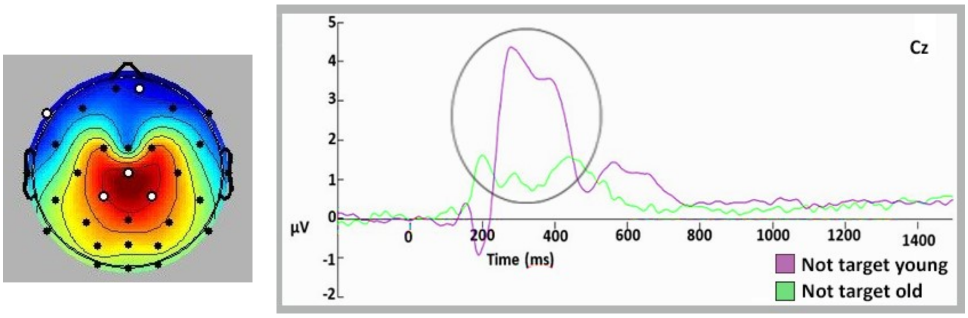


Figure 52 The first figure shows the t test with correction for multiple comparisons results. The dots on the scalp represent the electrodes; the black ones were not statistically significant in the comparison carried out, while the white ones were. The red and blue colours represent the activation: the red one means that the second item is less active than the first, while in the blue one the second item is more active than the first.

The second figure shows the component found at Cz electrode in the non target condition in the young and old groups. On the y-axis the amplitude (micron volt) is shown, while on the x-axis the time (milliseconds) is represented. The light violet line represents the non target condition in the young group, while the green the non target condition in the old one.

3.3.3 Haemodynamic results

3.3.3.1 Oxygenated haemoglobin results

3.3.3.1.1 Within-group results

In both the adult and healthy elderly groups, the contrasts between all the conditions (control, low and high cognitive load) did not show any differences.

The comparison regarding the level of oxygenated haemoglobin in the two hemispheres did not show any differences.

3.3.3.1.2 Between-group results

The contrasts regarding the control condition and the low cognitive load one showed no differences due to age. On the other hand, in the high cognitive load one, the younger participants showed higher oxygenated haemoglobin in the channels 9 and 1 than the elderly (channel 1: M younger=.0024 ds=.2034; M elderly=-.0221, ds=,1255, p<.05; channel 9: M younger=.1080 ds=.2328; M elderly=.0233 ds=.2102, p<.05) (Figure 53). Channel 9 lies in the premotor cortex (Broadmann area 6) and in the dorsolateral prefrontal cortex (Broadmann area 9) (Koessler et al., 2009). Channel 1 lies in the middle frontal prefrontal dorsolateral cortex (Broadmann area 46) and in the frontal eye field (Broadmann area 8) (Koessler et al., 2009).

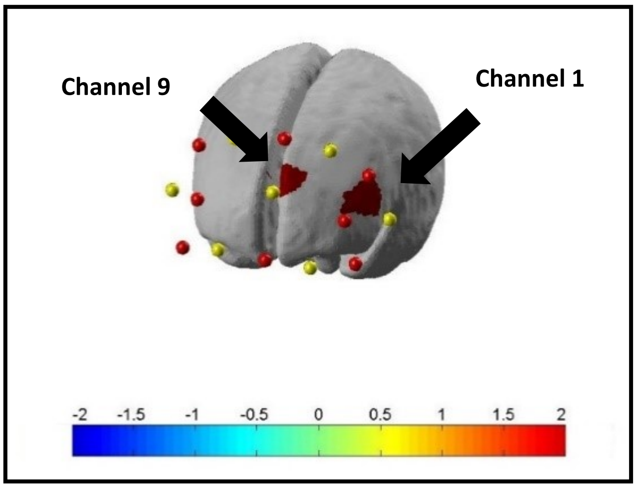


Figure 53 The result of the comparison between older and younger participants in the high load condition of the oxygenated haemoglobin. The red dots represent the emitters and the yellow dots represent the detectors. The red areas represent the channels that show a significant result in the comparison, with a p less than 0.05.

The comparisons regarding the oxygenated haemoglobin in left and right hemispheres were not different between the two groups.

3.3.3.2 Deoxygenated haemoglobin results

3.3.3.2.1 Within-group results

In both the adult and healthy elderly groups, the contrasts between all the conditions (control, low and high cognitive load) did not show any differences.

The comparison regarding the level of deoxygenated haemoglobin in the two hemispheres did not show any difference.

3.3.3.2.2 Between-group results

The control condition and the low cognitive load one were not different in terms of deoxygenate haemoglobin between the two groups. Nevertheless, like the oxygenate haemoglobin results, the high cognitive load condition showed an effect due to age: in channel 7 it was higher in the younger (M=-.02063 ds=.049343) than the older participants (M=-.001239 sd=.029973) (Figure 54). This channel lies in the dorsolateral prefrontal cortex (Broadmann area 9) (Koessler et al., 2009).

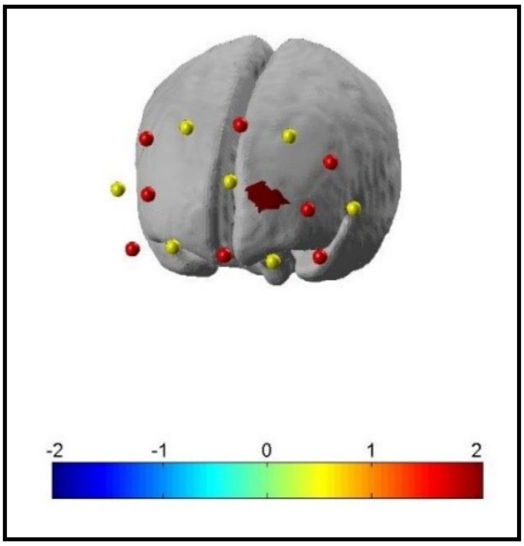


Figure 54 The result of the comparison between older and younger participants for the high load condition in the deoxygenated haemoglobin. The red dots represent the emitters and the yellow dots represent the detectors. The red area represents the channels that show a significant result in the comparison, with a p less than 0.05.

Finally, the level of deoxygenated haemoglobin did not differ between the groups in both left and right hemispheres.

3.3.4 Correlation between the data collected

3.3.4.1 Correlation between electrophysiological and behavioural data

The component P2 was not correlated with either accuracy or reaction time in younger and older participants.

Regarding the P3, the latency as well as the amplitude did not correlate with accuracy. Regarding the reaction time, two correlations were found. A negative one between amplitude and the control condition (r=-.510, N=31, p=.003) (Figure 55) and a positive one between all of them and the latency at Pz (r=.466, N=31, p=.008) (Figure 56).

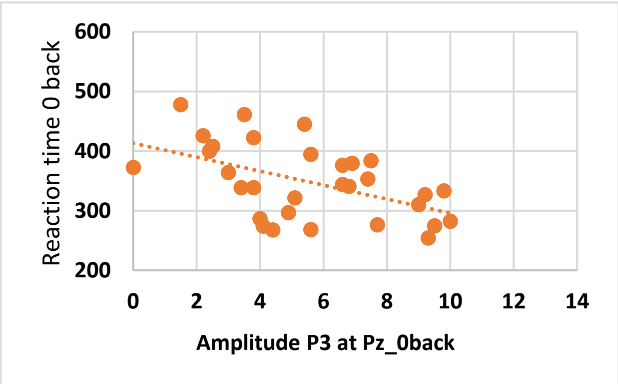


Figure 55 The negative correlation between the reaction time in the control condition (y axis) and the P3 amplitude at Pz (x axis) in the same condition.

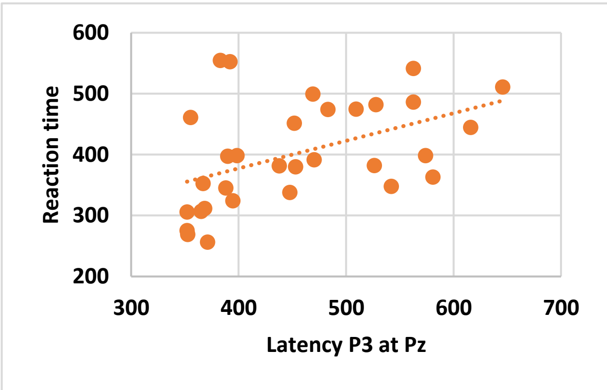


Figure 56 The positive correlation between the reaction time (y axis) and the P3 latency at Pz (x axis).

Lastly, no correlation was found between the N3 component in both reaction times and accuracy.

3.3.4.2 Correlation between haemodynamic and behaviour data

The oxygenated haemoglobin was positively correlated with accuracy in the highest cognitive load condition in channel number 9, which lies in the dorsolateral prefrontal cortex (r=.385, N=32, r=.029) (Figure 57).

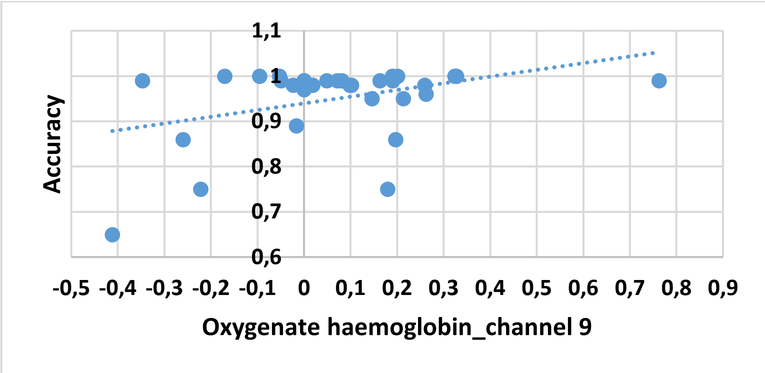


Figure 57 The positive correlation between accuracy in the high cognitive load condition (y axis) and the oxygenated haemoglobin in the 9 channel (x axis) in the same condition.

No correlation was found regarding the reaction time and the oxygenated haemoglobin, in any condition or channel.

The deoxygenated haemoglobin in the right hemisphere during high cognitive load condition was negatively correlated with accuracy (r=-.363, N=32, p=.041) (Figure 58).

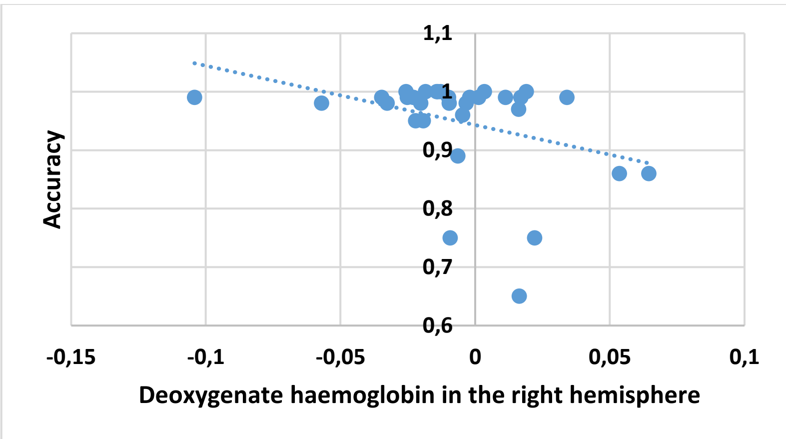


Figure 58 The negative correlation between accuracy in the high cognitive load condition (y axis) and the oxygenated haemoglobin in the right hemisphere (x axis) in the same condition.

No correlation between the deoxygenated haemoglobin and the reaction times was found.

3.3.4.3 Correlation between haemodynamic and electrophysiological data

The main purpose of this analysis was to better understand the oxygenated haemoglobin pattern. It showed an increase under the low cognitive load condition, compared to both the control and high cognitive ones (Figure 59). This pattern was similar in both groups, so the hypothesis that it was caused by ageing was discharged. A correlation between evoked potential results and fNIRS data was carried out in order to understand if the pattern found was due to an arousal artefact or to brain activity. Moreover, the deoxygenated haemoglobin was also correlated with the components found, in order to understand the relation between those two types of data, if any.

The components from the prefrontal channels were extracted, in order to have comparable data (since the fNIRS montage was only prefrontal). The evoked potential results of channels Afp1, Afp2, Aff5h, Aff6h, F7 and F8 were taken into account.

Two components were extracted, the P2 and the N3. The first one showed a different pattern compared to the fNIRS data: the amplitude increased as the quantity of information in the working memory increased. Instead, the N3 showed the same pattern as oxygenated haemoglobin: the amplitude was bigger in the low cognitive load condition compared to the other two. This pattern was detectable in both groups (Figure 60).

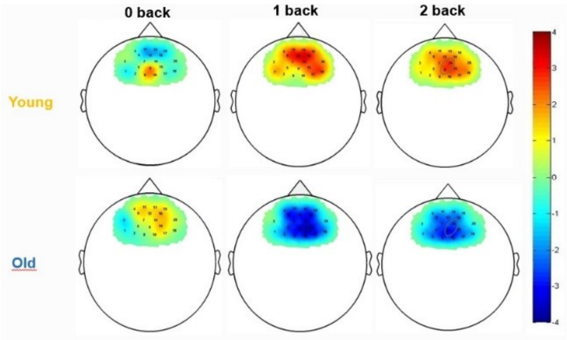


Figure 59 The oxygenated haemoglobin pattern in both younger (upper half) and older (downer half) participants in the three conditions.

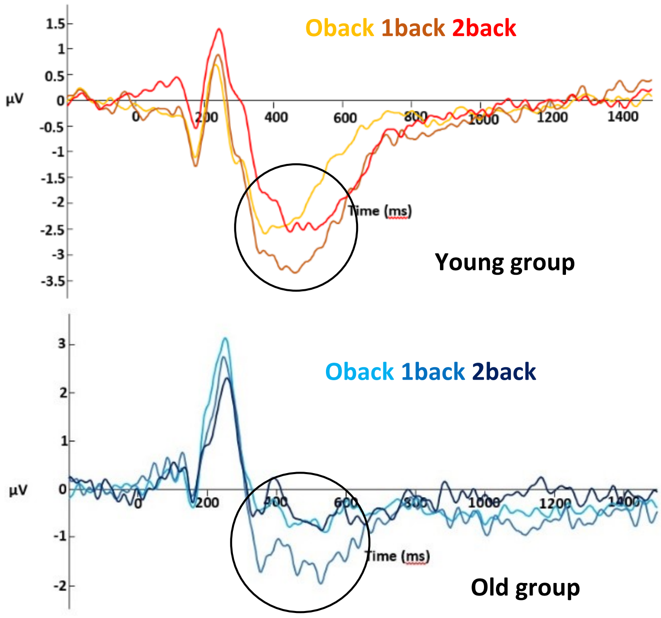


Figure 60 The N3 amplitude pattern in both younger (upper half part) and older (downer half) participants in the three conditions.

Correlation between the N3 component and oxygenated haemoglobin showed correlations only in the older participants group. In particular, a positive correlation between the amplitude of N3 and oxygenated haemoglobin in the 1 back condition was found [r(15)=.604, p=.017] (Figure 61).

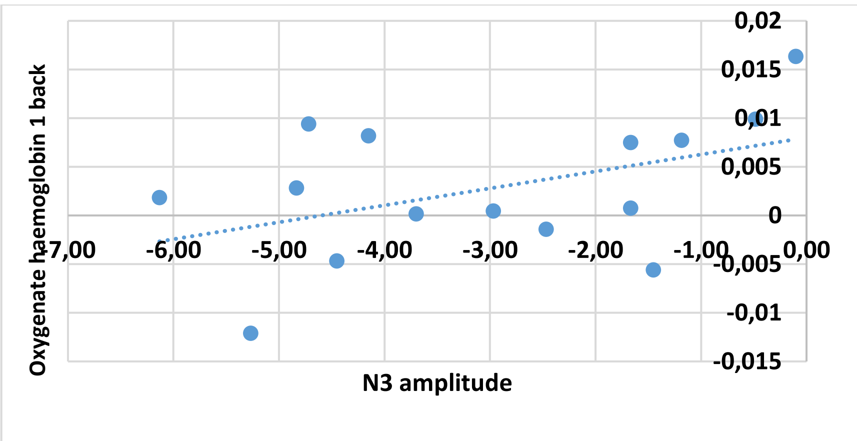


Figure 61 The positive correlation between the N3 amplitude (x axis) and the oxygenated haemoglobin in older participants (y axis) in the low cognitive load condition

The deoxygenated haemoglobin, like the oxygenated one, did not show any correlation with the N3 found in younger participants. Nevertheless, the older group showed a negative correlation between the amplitude of N3 and the deoxygenated haemoglobin in the right hemisphere [r(15)=-.532, p=.041] (Figure 62).

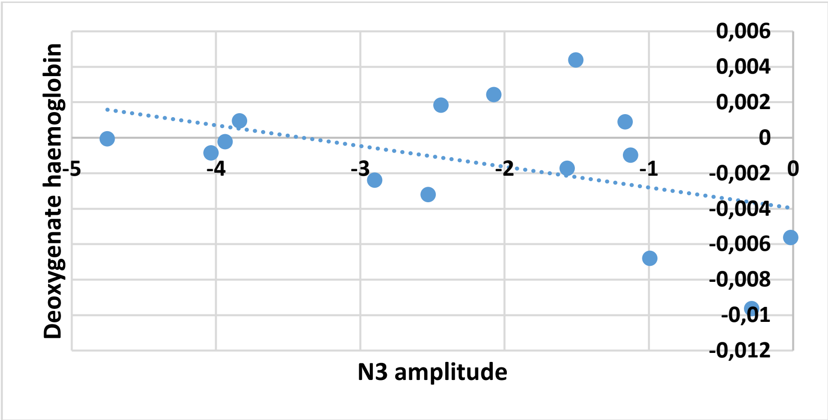


Figure 62 The positive correlation between the N3 amplitude (x axis) and the deoxygenated haemoglobin in older participants in the right hemisphere (y axis) in the low cognitive load condition.

3.4 Discussion

As expected, ageing affects visuo-spatial working memory and this effect was visible in all the correlates collected.

Regarding the behavioural results, accuracies and reaction times showed a different pattern. The former showed a decrease due to age only in the most demanding task. This was consistent with previous studies (Gajewski and Falkenstein, 2014; Mattay et al., 2006; Wild-Wall, Falkenstein and Gajewski, 2011). On the other hand, reaction times showed an increase due to age also in the control condition. This pattern was also found in the majority of previous works (Mattay et al., 2006; Missioner et al., 2004; Vaughan et al, 2008; Van Gerven, 2008; Gajewski and Falkestein, 2014) and seems to be due to a general decrement in speed, both related and not related to working memory.

The within-group analysis showed the effect of the cognitive load on the reaction time as well: in both groups they became slower as n increased. The two groups showed different accuracy results. In the younger group no difference between conditions were found; in the older group participants made more mistakes in the 2 back compared to control condition.

Regarding the electrophysiological results, no differences between groups were found, taking into account the high cognitive load. While in the low cognitive load condition and control one older participants showed more amplitude in the P2; this is consistent with some previous works (Anderson et al, 1996; Finningan et al., 2011). Ageing correlated with a compensation mechanism in the attention process, which seems to be independent from the response process. The P3b showed an age effect in the control condition: it was smaller in amplitude in the older participants. This was consistent with previous literature (Gajewsky and Falkenstein, 2014 (Wild-Wall, Falkenstein and Gajewski, 2011). Moreover, this result negatively correlates with reaction times, consistent with Gajewsky and Falkenstein’s work (2014). Ageing seems to be related to less allocation of cognitive resources (Polich, 2007) in the control condition. Regarding the target condition, the younger participants showed a detectable higher amplitude in the N3; consistent with previous work (West & Covell, 2006; Daffner et al. 2012) the elderly showed less maintenance compared to younger participants. Moreover, the latency of the P3 was found at a later moment in the elderly, which is related to a slower selection of the response. In the non target condition, in line with the results found in this and other works, age was correlated with less amplitude in both P2 (Anderson et al, 1996; Finningan et al., 2011) and P3 (Gajewsky and Falkenstein, 2014; Wild-Wall, Falkenstein and Gajewski, 2011), showing impaired attention and selection of response processes. More in detail, in this case, the P3 alteration is linked to an inhibitory process, since in this condition participants had to withdraw the response.

Regarding the within group results, no differences were found in the older participants, despite the ones found in the behavioural results. The evoked potential components found in younger participants showed an expected pattern, in which the higher cognitive load condition showed higher P3 and LPC amplitudes and latencies compared to the control one. Moreover, this condition showed less amplitude than the P2 and P3 amplitude in the low cognitive load one. This is explainable by the fact that it is linked, as the tasks' difficulty increases, to more attention being needed (P2) (Finningan et al., 2011); an higher memory response due to more items that have to be remembered (LPC) (Garcia-Laerra & Cezanne-Bert, 1998) and higher amplitude in the selection of response process (P3) (Watter et al., 2001; Luu et al., 2014). The comparison between target and non target, showed a higher than expected amplitude in the P3 of the target one, supporting once again, the role of this component in the response process.

In the haemodynamic result, younger participants showed more activation in both oxygenated and deoxygenated haemoglobin. The effect in both case was related to more activation in the premotor and dorsolateral prefrontal cortex and frontal eye field. Moreover, in the deoxygenated haemoglobin it correlates with the reaction time. Regarding the premotor results found, this can be explained as a decrease due to age in the selection of the response (Purves et al., 2001). The other effect is clearly due to the dorsolateral part of the prefrontal cortex and it is consistent between both oxygenated and deoxygenated measures. This portion of the prefrontal cortex is linked to motor regions (which support the previous results found) and the primary sensory region as well as parietal one (MacPherson et al, 2002). In addition, the frontal eye field is part of the dorsolateral prefrontal cortex and is related to localization of the target (Schall, 2009). This distinct activation supports an effect specific to working memory, since other regions that are part of prefrontal area were not activated; those region are related to other functions, that would have confounded the data, for example the ventrolateral prefrontal cortex activation is due to emotional responses (MacPherson et al, 2002). Since the n back task could generate an activation due to emotional responses more than working memory per se (Ito et al., 2011), it is remarkable to have found a specific activation of an area considered linked to working memory (Petrides & Milner, 1982). In particular, literature about ageing has failed to consider this specific activation, talking in general about the prefrontal effect of age (Daigneault & Braun, 1993; Moscovitch & Winocur, 1995 in MacPherson et al, 2002). Moreover, this area is more sensitive than the ventromedial one to ageing decline and this explains why in this study, this decline is also found in healthy and highly educated participants (MacPherson et al, 2002).

No hemispheric effect was found, in contrast to previous works (Vermeji et al, 2012).

The data found, moreover, was not due to arousal artefacts, since both deoxygenated and oxygenated showed a specific working memory cortex activation and a correlation with an evoked potential component related to selection of response, in the oxygenate data was found. This correlation was found only in older participants

Three limitations were present in this work. The first one is related to the fNIRS montage. In order to have a more detailed picture of the ageing effects on working memory, parietal channels would also be needed. This is because in oxygenated haemoglobin correlates the low cognitive load showed higher prefrontal activity than the high cognitive load one, but this seems to be related to an increase in parietal activation during the tougher condition (Cui et al., 2011). This was outside the aim of this work but in order to have a complete aging effect, that data is also needed. Moreover, regarding the fNIRS experimental design, a block one may not be the best option to correlate with evoked potential results. In order to have the same data, an evoked stimulus experimental design in the fNIRS collection of data is needed. Finally, the 2 back condition showed slower reaction times and higher errors compared to the others two; this could have a negative influence on the fNIRS data, since they are collapsed into blocks correlates. In the 2 back block is not possible to divide between the effect caused by ageing and the effect caused by ageing. In order to see the effect of both an evented-related design is needed.

In conclusion, healthy ageing impairs the selection of the response mechanism as well as the working memory one, which is formed by maintenance and updating processes. Those changes are visible in behavioural, hemodynamic and electrophysiological correlates.

CHAPTER FOUR

Visuo-spatial working memory in Parkinson’s disease: do high educational level and cognitive reserve have a positive influence?

4.1 Introduction

As was reported in previous chapters, working memory is negatively affected by age. This is true for healthy aging and a pathological one as well. In particular, one interesting pathology that can help to understand more about the working memory process is Parkinson’s disease.

The incidence of Parkinson’s disease is 10 million people worldwide (Parkinson’s disease foundation) while the incidence increases with age; only 5% show the disease before the age of 50 (Parkinson’s disease foundation).

Parkinson’s disease is mainly, but not only, characterized by motor disorders, such as tremor, rigidity, bradykinesia and difficulty in maintaining posture (Rottschy et al., 2013). Other symptoms include REM-sleep behaviour disorder (they behave during the day in the same way as during REM sleep phase) depression and hyposmia that can pre present already in the pre-clinical period (Braak et al., 2003 in Rottschy et al., 2013). Moreover, patients show cognitive symptoms related to a deficit in executive functions: planning, the use of rules, the formation of the concepts and working memory (Taylor, Saint-Cyr& Lang, 1986 in Rottschy et al., 2013).

The deficits in cognitive functions and symptoms are related to dopamine neurotransmitter decrease. Dopamine receptors are present in both anterior and posterior parts of the brain, but the majority of them are situated in the prefrontal cortex. More in detail, mesocortical and mesolimbic dopaminergic system are present in the midbrain (more precisely, in the ventral tegmental area) and they project to the prefrontal cortex (Goldman-Rakic, 1990; Goldman-Rakic, 1992; Goldman-Rakic, 1995 in Cools &

D'Esposito, 2011) as well as the anterior cingulate cortex and anterior temporal lobe (hippocampus, amygdala and entorhinal cortex) (Arnsten AFT, 1998; Cools & Robbins, 2004; Cools & D'Esposito, 2009; Floresco & Magyar, 2006; Bannon & Roth, 1983; Shohamy & Adcock, 2010; Brown, Crane & Goldman, 1979 in Cools & D'Esposito, 2011). Animal studies find similar results. Brozosky et al. (1979) in Goldman-Rakic (1995) showed that dopamine depletion in the prefrontal cortex of rhesus monkeys was related to a deficit in working memory performance. Moreover, other studies found that this decrement in performance was specific for this neurotransmitter, since the same results were not found during the depletion of others, such as serotonin; finally, when treated with dopamine agonist the deficit disappeared (Brososki et al., 1979; Arnsten et al., 1994 in Leroi et al., 2013).

The working memory deficit seems to be the most important one (Owen et al., 1992; Dubois & Pillon, 1997 in Rottschy et al., 2013). It is related to the representation of the task as well as updating sub processes (Cohen, Braver & Brown, 2002; Bilder et al., 2004; D'Esposito, 2007 in Cools & D'Esposito, 2011). Working memory is formed by subcomponents: the phonological loop is related to the language process; visuo-spatial sketchpad is related to the management of both visual and spatial characteristics and episodic buffer is related to the maintenance of daily life scripts. All of these components are managed by the central executive (Baddeley, 2000; Baddeley, 2003) (for a more detailed description of the subcomponent refer to the first chapter).

Among them, the visuo-spatial one seems to be the most impaired (Bradley, Welch and Dick 1989; Fournet et al., 2000; Owen et al., 1993). Moreover, this deficit also remains when the patients are under medication.

Fournet et al. (2000) tested participants with Parkinson's disease on medication (L-dopa) in three different working memory tasks: a verbal one, in which they have to remember words; a visuo-spatial one, in which they have to remember the position of the words; and one related to the central executive, in which they have to remember both. The results showed that patients were more impaired in the visuo-spatial tasks and in the double ones (Fournet et al., 2000). The same participants were also tested off medication; the withdrawal of medication had an effect on the central executive task, while there were no changes in the other two (Fournet et al., 2000). Bradley, Welch and Dick (1989) used one verbal and one visuo-spatial tasks; comparisons between them and between on and off medication groups were carried out. No differences were found, but when the tasks required active manipulation of the stimuli (remembering and reporting them), the experimental group was slower in the visuo-spatial task but not in the verbal one, compared to the control group. Owen et al. (1998) compared patients and controls participants in the Tower of London task during PET registration; four conditions were analysed: simple planning (three moves solution), complex planning (four or five moves problem), simple spatial working memory (three guided moves), and complex spatial working memory (four or five moves solution). The simpler conditions was used as baseline. A control condition was also present. In all the conditions of the task participants performed worse than healthy participants. When patients and controls were compared directly, no differences in the prefrontal activation were found. However, the globus pallidus in the right hemisphere showed an inverse pattern between the groups: while in the control group it increased during tasks, the Parkinson's participants showed a decrease. This difference could be related to an increment of the inhibition in the areas not related to the task (Owen et al., 1998).

Similar results were found in another work that compared Parkinson's patients with control in a visuo-spatial and object working memory task. The task consisted of recognizing and responding if the stimulus presented was the same as the previous one; the instructions asked participants to be accurate. Generally, patients had less recognition discriminability. Moreover, they showed impaired performance in the visuo-spatial task, while in the object one they had the same results as the control group (Possin, Song & Salmon, 2008). Both the mood state and the results in the pure movement task were not correlated to the performance (Possin, Song & Salmon, 2008).

Owen et al. in 1993 compared patients on (anti-cholinergic medications) and off medication (patients in the beginning of the pathology) in the CANTAB battery and they found no difference in the recognition task (only participants in the latest stages of Parkinson's showed impairment in this task); the same was true for the simultaneous matching task. The groups differed only in the spatial working memory test; the more advanced the Parkinson's was, the worse the performance. This test seems to be the most sensible way to detect the Parkinson's pathology stages (Owen et al., 1993).

One task widely used in order to investigate working memory is the n back one (for more information see Chapter 1). One study used it and found differences between patients and control participants. Leroi et al. in 2013 compared Parkinson's disease participants on and off medication and found that, among all the tasks (Wisconsin, Trial making test, Stroop task, short term memory task and FAS), only the n back, with numbers as stimuli, showed a decreased performance in the experimental groups. The impaired cognitive focus and preserved cognitive flexibility in both groups (on and off medication) may be due to different neural underpinnings; the first one associated with dopamine function in the prefrontal cortex, while the second one could be related to striatum, not affected by the pathology (Bilder, Volavka, Lachman, & Grace, 2004 in Leroi et al., 2013). Rottschy et al. (2013) used a similar paradigm, in which participants had to report a sequence of dots during an fMRI measurement; the number of dots to remember and the time between stimuli and the responses varied between trials. The experimental group had less accuracy than the control one and both groups were affected by memory load condition (Rottschy et al. 2013). Regarding the fMRI results, the Parkinson's disease participants showed reduced activity in the putamen, bilateral temporal gyrus, bilateral superior parietal cortex, pre and primary motor cortex, bilateral inferior frontal gyrus, right precuneus, SMA, and right inferior parietal cortex (Rottschy et al. 2013). In the short recall period, the experimental group showed reductions in the left precentral gyrus, bilateral dorsal precentral gyrus, bilateral superior parietal lobule, left putamen and left intraparietal sulcus (Rottschy et al. 2013). While, in the longer recall period, they showed less activation in the left putamen, superior parietal cortex and precentral gyrus, as well as in the bilateral SMA and more activation in the right inferior frontal gyrus, posterior midline, including the retrosplenial cortex and the left medial superior parietal cortex (Rottschy et al. 2013). The putamen is related to maintenance and spatial motor working memory (Cairo, Liddle, Woodward & Ngan, 2004; Sadeh et al., 2001 in Rottschy et al. 2013) and the posterior cortex is related to high cognitive demanding tasks (Cavanna & Trimble, 2006 in Rottschy et al. 2013). What emerges from this and other studies is that the most important impairment in working memory is the "memory-motor" transformation, that is the transformation of the working memory spatial information in an action, i.e. to respond by button press (Helmuth, Mayr & Daum, 2000; Ketcham et al., 2003; Seidler, Tuite & Ashe, 2007 in Rottschy et al. 2013). Increasing the load in the working memory as well as the time between the stimulus and the response enhanced the decrease in the response (Ketcham, Hodgson, Kennard & Stelmach, 2003; Yaguez, Lange & Homberg, 2006 in Rottschy et al. 2013).

In both normal and pathological ageing, cognitive reserve is a factor that can preserve, at least in part, the abilities. Successful aging in the cognitive reserve concept is due to activities that the person has been performing during his or her life (Stern, 2012). This is an active reserve and it is different from one postulated before, that argued that successful ageing was related to quantitative characteristics of the brain such as neurons and synapsis numbers and size (Stern, 2012). As reported by Stern in 2012, longitudinal studies highlight the fact that educational level as well as job and leisure time activities can partially prevent the age effect and can ameliorate the outcome in pathologies such as Alzheimer's disease, HIV, vascular injury, neuropsychiatric disorders, multiple sclerosis and Parkinson's.

Regarding Parkinson's disease, few studies have investigated this aspect.

Glatt et al. (1996) compared Parkinson's patients with and without dementia and found that one of the significant predictors for the dementia was the educational level (as well as the severity of motor deficit and the onset of the pathology before the age of 60). This study showed that education can modify the decline in Parkinson's disease and this could be due to a greater cognitive reserve (Glatt et al. 1996). Moreover, Wirdefeldt et al. (2005) studied a cohort of twins (this type of research is particularly suitable to see the effect of the pathology, since the environment and the genetic factors are the same in the control and experimental group), and highlighted that educational level had a positive effect on Parkinson's dementia prevention. This effect was only found when comparing participants afflicted by the disease with the control group and this seems to reflect the fact that educational level is also related to genetic and familiar factors (Wirdefeldt et al. 2005).

Finally, in 2012, Berryhill & Jones, investigated the effect of the stimulation, by transcranial direct current stimulation (tDCS), in prefrontal cortex in old participants. A control condition (sham) was compared with anodal stimulation (excitatory) in two sites of the prefrontal cortex (right and left) during verbal and visual working memory tasks. Moreover, participants were divided by educational level, into two groups (one with high and one with low educational level). Results showed that only participants with high educational levels benefit from the tDCS and improve performance; the improvement was present for both the task and from both the stimulation site (Berryhill & Jones, 2012). In the participants with lower educational levels, no effect or a worse one was seen, in both tasks and both sites of the tDCS (Berryhill & Jones, 2012).

Since the effect of cognitive reserve in Parkinson's disease has not been studied per se in the literature, one study that compared patients with high educational levels with matched control participants was carried out in order to verify if this can compensate for the negative consequences due to the illness. Moreover, since it is highlighted that the most pronounced effect of the pathology is visible in visuo-spatial working memory, an n back task was carried out. Parkinson's disease participants could have a similar outcome as control group, in a high pathology sensitive task, thanks to the effect of the cognitive reserve.

4.2 Method

4.2.1 Participants

The experimental group consisted of 20 participants with Parkinson's disease. They were recruited through a Parkinson's association. The decision to recruitin participants there was due to the fact that normally most of the people that joined these activities have a high educational level. The age ranged between 57 and 81 years and the educational level between 5 and 24 years. The group was formed of 12 males and 8 females. The control participants were matched by gender, age and educational level (Table 3).

Exclusion criteria were: abnormal or uncorrected vision, a score in MMSE below 24 (Folstein, Folstein, & McHugh, 1975), a FAB score below 12 (Appollonio et al., 2005), history of neurological disorders, psychiatric illness, report of depression or anxiety, use of psychotropic medications. Four participants (two males and two females) were excluded because of a MMSE below 24, so the experimental and control groups were formed of 10 males and 6 females.

The number of years since diagnosis ranged from 3 to 17, but, since they were not related to either reaction time [r(=.332, N=16 p=.208)] or accuracy [r=-.047, N=16 p=.864] results, they were not considered a factor in the statistical analysis (Table 3).

All the participants were on medication (Table 4).

	Age	Educational level	Cri total score	Cri-education	Cri-work activity	Cri-leisure time	MMSE	FAB	MoCa	Digit span Forward Backward
Control group	68.08 ±7.06	10.67 ±7.47	108.17 ±20.45	100.84 ±23.14	102.18± 28.66	114.83 ±19.21	28.15± 1.76			
Parkinson's disease group	70.62 ±6.49	12.87 ±4.36	115.56 ±19.73	113.19 ±16.17	109.44 ±2.17	112.62 ±26.73	27.12 ±1.52	16.25 ±1.53	25.69 ±3.05	6.19 ±0.54 4.46 ±0.73

Table 3 The characteristics of the control and Parkinson's disease groups.

Participant	Years from diagnosis	Medication
1	7	Requip, Jumex, Sinemet
2	7	Madopar
3	9	Mirapexin, Sirio, Azilect
4	12	Sirio, Jumex
5	7	Stalevo, Requip
6	16	Sirio, Requip
7	3	Requip, Jumex, Sinemet
8	19	Sinemet, Sirio, Requip
9	6	Azilect, Requip, Sinemet
10	15	Stalevo, Mirapexin, Sinemet
11	3	Madopar, Requip, Jumex
12	5	Azilect, Madopar, Neupro-Rotigotina
13	3	Madopar, Requip, Azilect
14	4	Requip, Sinemet
15	6	Stalevo, Azilect, Sirio
16	17	Stalevo

Table 4 The years from diagnosis and medications of the Parkinson's participants.

4.2.2 Task and tests

The task and the test were the same used in the previous studies (for detailed description see paragraph 2.2.2).

To the experimental group other tests were administered as well.

The frontal assessment battery (FAB) (Dubois et al., 2000) is used in order to investigate frontal lobe dysfunction (The test is reported in the appendix). It is formed of six sub parts. The similarities part investigates the ability of conceptualization; the experimenter reads two words and the patients should explain what they have in common. The lexical fluency part allow us to investigate the strategies that the participant uses to recall the number of names starting with a certain letter in the minute of time given to complete the task. The programming part consists of reproducing the same series of movements made by the clinician or the experimenter. The insensitivity to interference part investigates the ability to perform a task with conflicting instructions. The inhibitory control task is a typical go and no-go one, in which participant has to withdraw a high activated response. Finally, the environmental autonomy task investigates the ability to suppress prehension. For each item mark is given between 0 and 3, based on the correctness of the response and the total is corrected for age end educational level (Appollonio et al., 2005).

The Montreal cognitive assessment (MoCa) test is well-suitable for the diagnosis and investigation of Parkinson's disease (Dalrymple-Alford et al, 2010) (The test is reported in the appendix). It is a rapid screening for mild cognitive dysfunction. It is formed of several sub tests; the first one is a shorter version of the trial making test, in which a series of numbers and letter should be alternately linked in a scalar order. There are two visual-constructive tasks: in one the participant has to copy a cylinder, while in the other, he or she has to draw a clock, with the numbers in the correct position and the hour at ten past nine. In the naming sub-task, the participant has to identify three animals drawn on a sheet of paper. Then a memory task is submitted, a series of names should be remembered by the patient immediately and at the end of the test. In this period of time, participants performed the digit span; in the digit span forward he or she had to repeat increasing series of numbers read by the experimenter. When two errors were made consecutively, the total amount of numbers remembered is the span. The same procedure is true for the digit span backward, but in this case the number should be repeted from the last to the first.

4.2.3 Procedure

All the participants were tested in the afternoon, in order to control for possible differences during the day in the performance.

Firstly, in order to avoid any possible fatigue effect, the visuo-spatial working memory test was carried out. Successively, the MMSE, MoCa, FAB, Digit span and Cri-q tests were administerred.

4.3 Results

Generalized linear mixed effect model was applied to the accuracy analysis and a generalized linear model to the reaction time. This analysis has several advantages. Instead of considering the number of participants, it is possible to take into account each trial and this increase the statistical power; in this case, instead of considering 32 participants, 17664 observations was taken into account. Moreover, this analysis combines the positive effect of the linear mixed model (excluding the random effects) with that of the generalized mixed model one, which works also with non-normal distributed data (Bolker et al., 2008). Finally, using this analysis it is possible to take into consideration more than one predictor at the same time (Baayen, Davidson & Bates, 2008).

Due to these positive aspects, this analysis is used nowadays in different disciplines, such as general science, medicine and engineering (Faraway, 2006; Fielding & Goldstein, 2006; Gilmour, Thompson, & Cullis, 1995; Goldstein, 1995; Pinheiro & Bates, 2000; Snijders & Bosker, 1999 in Baayen, Davidson & Bates, 2008).

The first step of the analysis consisted of highlighting the random effect. Then a series of models were created in order to explain the data and, finally, they were compared to each other using Anova analysis (Wagenmarkers & Farrell, 2004). If the Anova showed a significant comparison, the best model was chosen by the AIC value. It gives an estimation of the information lost; the less information that is lost, the smaller is the number given as result (Akaike, 1973, 1974, 1978, 1979, 1983, 1987; Bozdogan, 1987; Burnham & Anderson, 2002; Parzen, Tanabe, & Kitagawa, 1998; Sakamoto, Ishiguro, & Kitagawa, 1986; Takane & Bozdogan, 1987 in Wagenmarkers & Farrell, 2004; Dayton, 2003; Wagenmarkers & Farrell, 2004; Dayton 2003).

The analysis were done with the lme4 package (Bates, Maechler & Bolker, 2012) using r software (R Development Core Team, 2010).

The model takes into consideration possible differences due to pathology in accuracy and reaction times, as well as cognitive load. Moreover, the cognitive reserve results were also taken into account: the one based on educational level, as well as the one due to job, the one due to leisure time activities and the total one. Moreover, the results of the neuropsychological test MMSE, MoCa, Digit span backward and forward and FAB, were taken into consideration too.

4.3.1 Accuracy results

The analysis showed that only the subjects was a random effect, while the blocks, the trials and the stimuli were not. Therefore, the subject random effect was taken into account in each model tested.

The first comparison tested the effect of the pathology on the accuracies, but no differences between control group and Parkinson's disease one (AIC=6557.9) and null model (AIC=6556.2) were found (p=.58) (Figure 64a). The accuracies were equal between the control group (M control condition=0.99 sd=0.7; M low cognitive load=0.97 sd=0.18; M high cognitive load=0.83 sd=0.37) and the Parkinson's disease one (M control condition=0.98, sd=0.11; M low cognitive load=0.97, sd=0.17; M high cognitive load=0.87, sd=0.33) (Figure 64b).

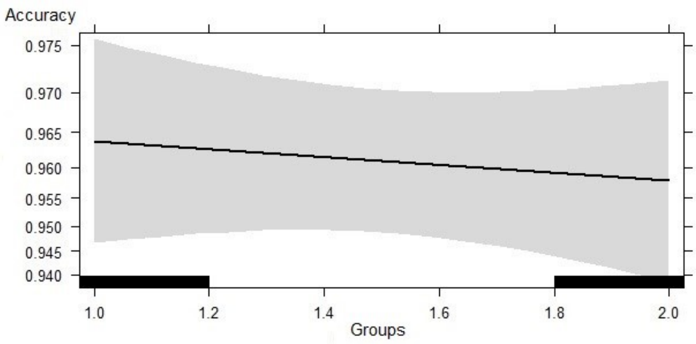


Figure 64a The absence of the group effect (y axis) on accuracy (x axis). The black rectangles represent the groups, the black line the effect per se and the grey bar the confidence interval

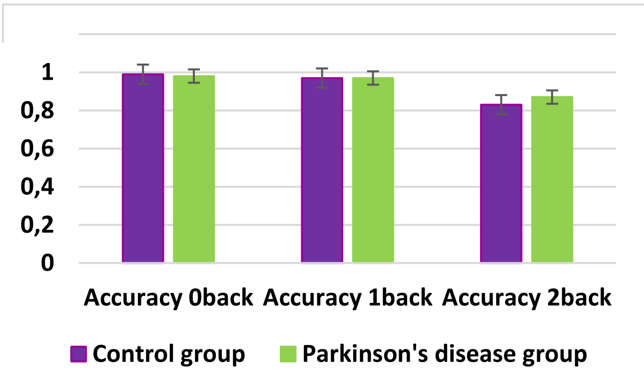


Figure 64b The accuracy results in each condition in each group. The violet columns represent the control group, while the green ones the experimental one.

The number of years since the diagnosis were tested in two different analysis. In the first one they were correlated with the test results, both in the different conditions of the n back task [control condition: r=-.243 n=16 p=.364] [1 back condition: r=.308 n=16 p=.246] [2 back condition: r=-.004 n=16 p=.987] and in the mean of them [r=.332 n=16 p=.208]. No correlation was found. The second one tested the model with the years since diagnosis (AIC=3071.3) and the null one (AIC=3069.4), but also in this case no differences between the two models were found (p=.774).

The gender effect as well as the condition one were taken into account.

There was no effect due to gender in the accuracy results (AIC null model=6556.2; AIC gender model=6557.6, p=.448).

Regarding the conditions effect, the model which contained them (AIC=6363.9) better explained the results than the null one (AIC=6552.8); this means that a higher increase in the cognitive load is related to a decrease in accuracy.

Regarding the effect of age (AIC age model=6546.4, AIC null model=6556.2, p<.001) and educational level (AIC educational level=6552.8, AIC null model=6556.2, p=.020) both of them had effects on the accuracy results. However, since they were not different between the groups (control group: M age=68.08, ds=7.06; M educational level=10.67, sd=7.47) (Parkinson's disease group: M age=70.62, ds=6.49; M educational level=12.87, sd=4.36) [t(29.932)=0.199, p=.844] [t(25.193)=0.790, p=.437], the effect found was general.

The cognitive reserve results showed similar effects.

The model that contained the total cognitive reserve (AIC=6236.7) explained the data more than the null one (AIC=6240.1) (p=.020). Higher was the total score at the Cri-q, higher the accuracies were (Figure 65). However, since it was not different between the groups (M control group=108.17. sd=23.14; M Parkinson's disease group=115.56, sd=19.73) [t(27.483)=0.348, p=.732] the effect found was general.

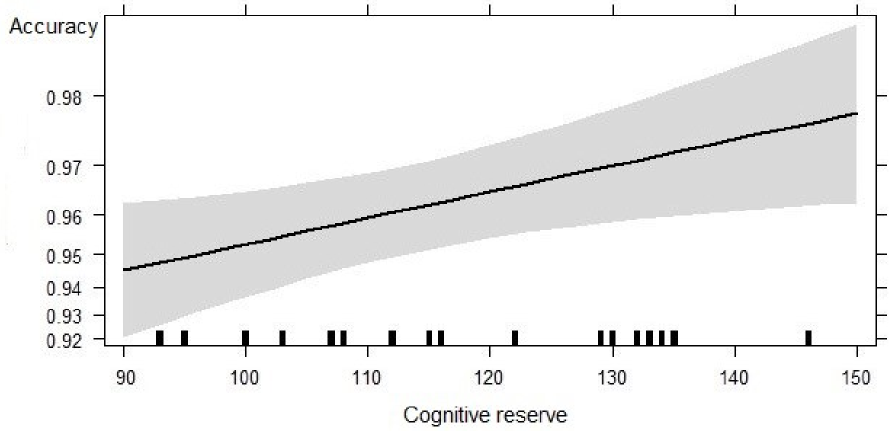


Figure 65 The increase of the accuracy (y axis) due to the increase in the cognitive reserve (x axis). The black squares represent the participants, the black line the effect per se and the grey bar the confidence interval

The model that contained the score relative to the cognitive reserve due to education (AIC=6239.9) did not explain the accuracy data found more than the null model (AIC=6240.1) (p=.136). The same pattern was found for the cognitive reserve due to leisure time (AIC cognitive reserve due to leisure time=6239.7; AIC null model=6240.1) (p=.117).

On the other hand, the model that contained the cognitive reserve due to job (AIC=6233.9) explained more than the control one (AIC=6240.1) (p=.004). The cognitive reserve due to job did not differ between the groups; this means that the effect found was general (M control group=102.18 ds=28.66; M Parkinson's disease group=109.44 ds=20.17) [t(28.283)=0.275, p=.785] (Figure 66).

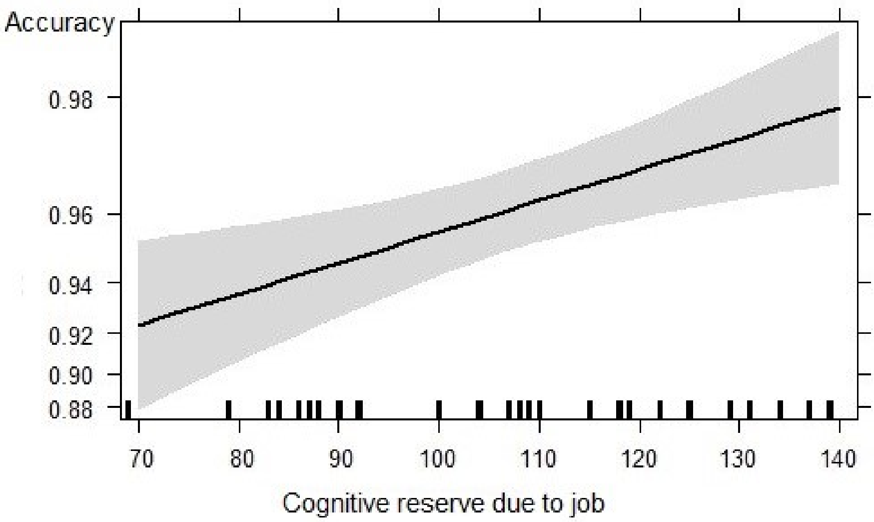


Figure 66 The increment of the accuracies (y axis) due to the cognitive reserve due to job (x axis). The black squares represent the participants, the black line the effect per se and the grey bar the confidence interval

Finally, none of the other tests administrated explained the accuracies results.

No differences were found in MMSE (AIC null model=5605.2; AIC MMSE model=5605.6, p=.213), as well as digit span forward (AIC null model=3069.4; AIC digit span forward model=3071.3, p=.884), digit span backward (AIC null model=3069.4; AIC digit span backward model=3071.0, p=.550), FAB (AIC null model =3069.4; AIC FAB model =.07447, p=.550) and MoCa (AIC null model =3069.4; AIC MoCa model=3069.8, p=.205) tests.

4.3.2 Reaction time results

The random effect of subject, trial, block and sub block were tested and among them, only the first one was present.

The reaction time distribution showed a screw to the right. For this reason, the reaction time were logarithmically transformed, in order to have a Gaussian distribution.

The first analysis carried out was a comparison between the null model (AIC=1993.8) and the one which contains experimental and control groups (AIC=1992.4); no differences in reaction time were found due to the pathology (p=.096) (Figure 67a). The reaction time in control group (M control condition=6.08 sd=0.54; M low cognitive load=6.11 sd=0.36; M high cognitive load=6.42 sd=0.41) were not different from the Parkinson's group ones (M control condition=6.25 sd=0.37; M low cognitive load=6.26 sd=0.38; M high cognitive load=6.45 sd=0.42) (Figure 67b).

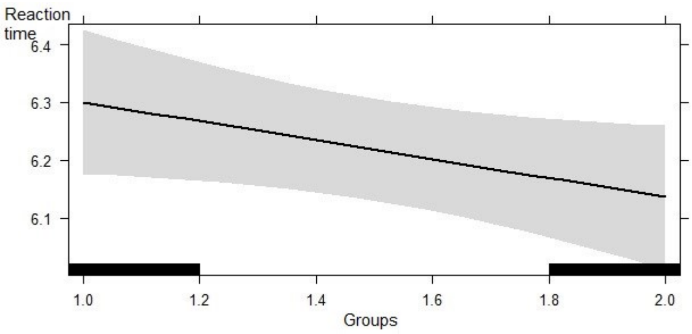


Figure 67a The absence of the group effect (y axis) on reaction time, logarithmically transformed (x axis). The black rectangles represent the groups, the black line the effect per se and the grey bar the confidence interval

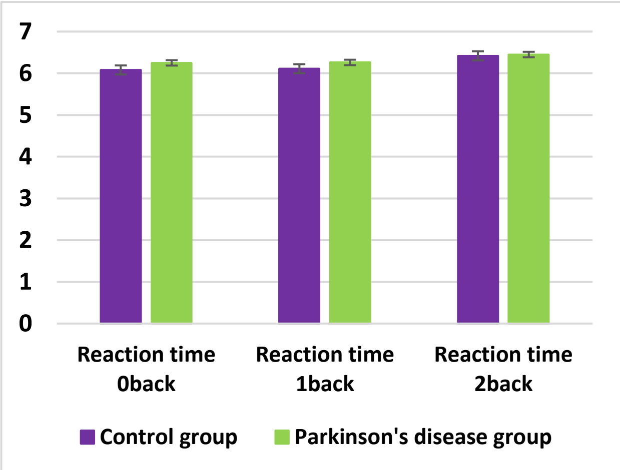


Figure 67b The reaction time logarithmically transformed results for each condition for each group. The violet columns represent the control group, while the green the experimental

Subsequently, the years since the diagnosis were analysed. Similar to the accuracies, no effect was found. More in detail, the model which contained the years from the diagnosis (AIC=665.06) did not explained more than the null one (AIC=663.16) (p=.757).

On the other hand, the conditions had an effect on the accuracies results: the model which contains them (AIC=973.71) explained more than the control one (AIC=1571.33) ($p<.001$). This means that when increasing the cognitive load (from control condition to 2 back) the participants, in both groups, became slower.

Age had an effect on accuracies pattern result as well (AIC null model=1571.3; AIC age model =1564.6 ($p=.003$). The effect found was present in general, since the age did not change between the groups (M Parkinson's disease group=70.62 sd=6.94; M control group=68.08 sd=7.06) [$t(29.932)=0.199$, $p=.844$].

Differently, the null model (AIC= 1571.3) was not different from the one that contained the educational level (AIC= 1572.4) ($p= .332$).

Finally, no effect of the gender was found; the model with the gender (AIC=1571.9) did not explained more than the null one (AIC=1571.3) ($p=.231$).

All the cognitive reserve results were taken into account.

The model with the total cognitive reserve score (AIC=6236.7) explained more the data found than the control one (AIC=6240.1) ($p=.044$). On the other hand, no differences were found between the model with cognitive reserve due to job and the null one (AIC null model=1571.3; AIC cognitive reserve due to job=1570.4, $p=.089$) (Figure 68).

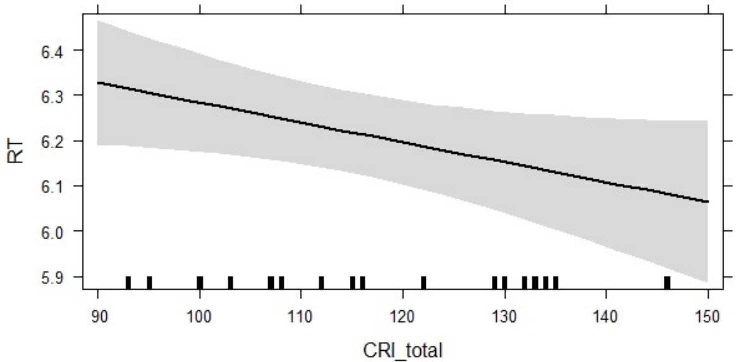


Figure 68 The decrement of the reaction times (y axis) due to the cognitive reserve total score(x axis). The black squares represent the participants, the black line the effect per se and the grey bar the confidence interval

Similarly to the accuracy results, both the cognitive reserve due to educational level, as well as the cognitive reserve due to leisure time models, did not explain the reaction time results. More in detail, the model that explained the cognitive reserve due to educational level (AIC=1572.8) did not differ from the null one (AIC=1571.3) (p=.4454). This one was also not different from the one that contained the cognitive reserve due to leisure time (AIC=1819.9) (p=.082).

Regarding the other test results, none explained the reaction time results. No effect were found in FAB (AIC null model=663.16; AIC FAB model=663.31, p=.174), MoCa (AIC null model=663.16; AIC MoCa model=663.88, p=.259), digit span forward (AIC null model=663.16; AIC digit span forward model=662.77, p=.123) and backward (AIC null model=663.16; AIC digit span backward model=662.70, p=.117).

4.4 Discussion

In both accuracy and reaction time no differences were found between the groups. The educational level, which was not different between the two groups, explained the accuracy found. This result is in line with the postulated hypothesis, which says that educational level prevent a decrease in the behavioural results due to Parkinson disease (Glatt et al.; 1996 Wirdefeldt et al., 2005; Berryhill & Jones, 2012). Differently from what was expected, the educational level did not explain the reaction time results. This was true for the job cognitive reserve as well, while it explained the accuracy results, it did not have an effect on reaction times. On the other hand, the total Cri-q score explained both reaction time and accuracy results. These results were consistent with Stern's theory of cognitive reserve (Stern, 2012). The job that both control and Parkinson's participants did or do as well as cognitive reserve have a positive effect on a working memory task. This is partially in line with the Berryhill & Jones (2012) study, which showed that high educational level had a positive effect on prefrontal cortex in Parkinson's disease. The same result was found regarding the accuracies, but not regarding the reaction time results.

The effects of ageing and cognitive load were consistent with the literature regarding the n back task and working memory in general (age effect: Vaughan et al, 2008; Van Gerven, 2008; Daffner et al., 2011; Nyberg et al., 2009; Vermeij et al., 2012; Voelcher-Rehage, Stronger and Alberts, 2006; Mattay et al., 2006; Missioner et al., 2004; Wild-Wall, Falkenstein and Gajewski 2011; Daffner et al., 2011) (cognitive load effect: Ragland et al., 2002; Chen, Mitra & Schlaghecken, 2008; Chen & Mitra, 2009; Raemae et al., 2001; Spronk & Jonkman, 2012; Tanaka et al., 2012; Leon-Dominguez, Martin-Rodriguez & Leon-Carrion, 2015; Alain et al., 2009; Callicott et al., 1999; Druzgal & D'esposito, 2001; Brower et al., 2012; Kim et al., 2003).

Regarding the non effect of the digit span, MoCa and FAS tests, it could be explained by the fact that the results founded were in the normal range.

In conclusion, visuo-spatial working memory in Parkinson’s patients with high educational level is preserved due to the cognitive reserve. However, while in the accuracies it is clear, in the reaction time it is less understood.

CONCLUSIONS

This work had the aim to fill the lack in the literature about how ageing influenced visuo-spatial working memory. Three different studies were conducted. The first two studies were carried out with healthy participants, while the third one investigated Parkinson's disease. This change was studied by behavioural, electrophysiological and hemodynamic correlates. The educational level and cognitive reserve were taken into account. In the first study were studied the effect of both, while in the second and third studies all the participants had the same educational level and cognitive reserve, in order to control these factors.

The first study had the aims of highlight when and how ageing effect on visuo-spatial working memory starts to be visible. For this reason healthy participants ranged from 20 to 80 years old were tested. The experimental design was cross-sectional. Moreover, also the educational level and different types of cognitive reserve (total score, cognitive reserve due to educational level, cognitive reserve due to job and cognitive reserve due to leisure time) were investigated. The results showed that both accuracy and reaction time showed aged effects, but the former starts to be visible first. More in detail the effect of aging on accuracy were become visible at 34 years, while on reaction times at 57. The effect in the accuracy was general, while in the reaction time an interaction between age and high demanding condition was found. Cognitive reserve had effects on the results found. More in detail, total score had a positive effect on accuracy and cognitive reserve due to educational level had a positive effect on reaction times. Have a higher educational level and a good cognitive reserve had a good influence on a visuo-spatial working memory task, regarding both the speed and the correctness. An unexpected result was found in the cognitive reserve due to leisure time, since it had a negative effects on results. This could be explained by the less time used for working and studying in participants with higher results in this measure.

The second study had the aim to highlight the ageing effects on visuo-spatial working memory. Behavioural, hemodynamic and electrophysiological correlates were recorded in adults and healthy elderly participants. Participants recruited were selected with similar educational level and cognitive reserve, in order to control for this variables. Different types of correlated were collected in order to have a complete picture of the phenomenon. Electrophysiological correlates were recorded in order to have information about the timing of the process, hemodynamic one in order to know more about the anatomical activation and behavioural one in order to test speed and correctness of the process and of the influence of aging on it. Moreover, all data was collected at the same time. This has the advantage of having different types of information from the same participants and with the possibility to understand the common processes between the different data collected; this generates a complete picture of how healthy aging affects visuo-spatial working memory. The results showed that, despite no differences between young and old participants in term of educational level and cognitive reserve, all the data collected showed negative effects due to age. The behavioural results showed a decrement in both reaction time and accuracies. The decrement in accuracy was detectable only in the high demanding condition (2 back). On the other hand, reaction time showed a general slowness in the elderly group. The neuroanatomical correlated showed a decrement in the dorsolateral prefrontal cortex and in the premotor cortex in the healthy elderly. The first region is related to the working memory functioning per se and the second one to the selection of response and to the transformation of responding mechanism in a finalized movement. Moreover, also the frontal eye field, related to target selection, showed a negative ageing effect. Regarding the electrophysiological results, no differences were found in the high cognitive load. On the other hand, in the control condition and in the low cognitive one, older participants showed an increment in the attentional response and a decrement in the selection of the response process. This correlated of the reaction times results. In the target condition, in which participants had to reply, elderly showed a decrement of the maintenance response. This correlated of the hemodynamic results found. This suggested that healthy ageing is correlated with a compensatory mechanism regarding the attentional process and with impairments in maintenance and selection of response ones. This pattern is consistent among behavioural, hemodynamic and electrophysiological correlates.

The last study compared healthy participants with Parkinson’s disease patients. No differences in reaction times and accuracy were found. Instead, positive effects of educational level and cognitive were found. Detailed, total cognitive reserve score had a positive influence on both reaction time and accuracy, independently being healthy or with Parkinson’s disease. Moreover, cognitive reserve due to job had a positive effect on the accuracy results. Since the participants were selected with similar educational level and cognitive reserve, the similar results in both accuracy and reaction times could be explained by positive effect of cognitive reserve.

This thesis showed that visuo-spatial working memory is negatively affected by ageing, but also that high educational level and cognitive reserve could have a positive effect on these changes. Educational level and cognitive reserve showed a positive effect not only in the healthy ageing, but also in Parkinson’s disease patients.

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APPENDIX

ANIMAL NAMING TEST

Introduzione: "Sarebbe disponibile a fare un breve test di prontezza e memoria?"

Istruzione: "Mi potrebbe dire quanti più animali ricorda, il più velocemente possibile?" E' pronto? Bene, allora cominciamo!"

Procedura: Far partire il cronometro e registrare il numero di animali. Se il paziente si interrompe prima dei 60 sec, dirgli "Qualche altro animale?" Se il paziente tace per 15 sec, dire "il cane è un animale. Può dirmi altri animali?"

Punteggio: contare gli animali, non includendo animali ripetuti o vocaboli non attinenti ad animali

1. ________________________	18. ________________________	35. ________________________
2. ________________________	19. ________________________	36. ________________________
3. ________________________	20. ________________________	37. ________________________
4. ________________________	21. ________________________	38. ________________________
5. ________________________	22. ________________________	39. ________________________
6. ________________________	23. ________________________	40. ________________________
7. ________________________	24. ________________________	41. ________________________
8. ________________________	25. ________________________	42. ________________________
9. ________________________	26. ________________________	43. ________________________
10.________________________	27. ________________________	44. ________________________
11.________________________	28. ________________________	45. ________________________
12. ________________________	29. ________________________	46. ________________________
13. ________________________	30. ________________________	47. ________________________
14. ________________________	31. ________________________	48. ________________________
15. ________________________	32. ________________________	49. ________________________
16. ________________________	33. ________________________	50. ________________________
17. ________________________	34. ________________________	51. ________________________

Scoring: contare il numero totale di animali (NON includere animali ripetuti o parole che non siano animali). Vanno inclusi uccelli, pesci, rettili, insetti, animali estinti, ecc. Sono corretti anche i termini relativi alle categorie (es: cani, mammiferi). Nel caso di nomi relativi allo stesso animali in fasi diverse dello sviluppo, va considerato un solo punto (es: pecora, agnello): __________

Se il punteggio è <u>inferiore a 14</u> dovrebbero essere effettuati ulteriori test

Sager MD, MA; Hermann PhD, BP; LaRue PhD, A; Woodard PhD, JL, Screening for Dementia in Community-based Memory Clinics. Wisconsin Medical Journal 2006.105(7)25-29

BECK DEPRESSION INVENTORY-2

Istruzioni. Il presente questionario consiste di 21 gruppi di affermazioni. Per favore legga attentamente le affermazioni di ciascun gruppo. Per ogni gruppo scelga quella che meglio descrive come Lei si è sentito nelle *ultime due settimane* (*incluso oggi*). Faccia una crocetta sul numero corrispondente all'affermazione da Lei scelta. Se più di una affermazione dello stesso gruppo descrive ugualmente bene come Lei si sente, faccia una crocetta sul numero più elevato per quel gruppo. Non scelga più di una affermazione per ciascun gruppo, incluse la domanda 16 ("Sonno") e la domanda 18 ("Appetito"). È importante che non ci sono risposte giuste o sbagliate. Non si soffermi troppo su ogni affermazione: la prima risposta è spesso la più accurata.

1. Tristezza

0. Non mi sento triste.
1. Mi sento triste per la maggior parte del tempo
2. Mi sento sempre triste
3. Mi sento così triste o infelice da non poterlo sopportare.

2. Pessimismo

0. Non sono scoraggiato riguardo al mio futuro.
1. Mi sento più scoraggiato riguardo al mio futuro rispetto al solito.
2. Non mi aspetto nulla di buono per me.
3. Sento che il mio futuro è senza speranza e che continuerà a peggiorare.

3. Fallimento

0. Non mi sento un fallito.
1. Ho fallito più di quanto avrei dovuto.
2. Se ripenso alla mia vita riesco a vedere solo una serie di fallimenti.
3. Ho la sensazione di essere un fallimento totale come persona.

4. Perdita di piacere

0. Traggo lo stesso piacere di sempre dalle cose che faccio.
1. Non traggo più piacere dalle cose come un. tempo.
2. Traggo molto poco piacere dalle cose che di solito mi divertivano.
3. Non riesco a trarre alcun piacere dalle cose che una volta mi piacevano.

5. Senso di colpa

0. Non mi sento particolarmente in colpa.
1. Mi sento in colpa per molte cose che ho fatto o che avrei dovuto fare.
2. Mi sento molto spesso in colpa.
3. Mi sento sempre in colpa.

6. Sentimenti di punizione

0. Non mi sento come se stessi subendo una punizione.
1. Sento che potrei essere punito.

7. Autostima

0. Considero me stesso come ho sempre fatto
1. Credo meno in me stesso
2. Sono deluso di me stesso.
3. Mi detesto.

8. Autocritica

0. Non mi critico né mi biasimo più del solito.
1. Mi critico più spesso del solito.

. Mi critico per tutte le mie colpe.

. Mi biasimo per ogni cosa brutta che mi accade.

9. Suicidio

0. Non ho alcun pensiero suicida
1.Ho pensieri suicidi ma non li realizzerei
2. Sento che starei meglio se morissi.
3. Se mi si presentasse l'occasione, non esiterei ad uccidermi

10. Pianto

. Non piango più del solito.

. Piango più del solito.

. Piango per ogni minima cosa.

. Ho spesso voglia di piangere ma non ci riesco.

11. Agitazione

0. Non mi sento più agitato o teso del solito.
1. Mi sento più agitato o teso del solito.
2. Sono così nervoso o agitato al punto che mi è difficile rimanere fermo.
3. Sono così nervoso o agitato che devo continuare a muovermi o fare qualcosa.

12. Perdita di interessi

0. Non ho perso interesse verso le altre persone o verso le attività.
1. Sono meno interessato agli altri o alle cose rispetto a prima.

2. Mi aspetto di essere punito. 3. Mi sento come se stessi subendo una punizione. **13. Indecisione** 0. Prendo decisioni come sempre. 1. Trovo più difficoltà del solito nel prendere decisioni. 2. Ho molte più difficoltà nel prendere decisioni rispetto al solito. 3. Non riesco a prendere nessuna decisione. **14. Senso di inutilità** 0. Non mi sento inutile. 1. Non mi sento valido e utile come un tempo. 2. Mi sento più inutile delle altre persone. 3. Mi sento completamente inutile. su qualsiasi cosa. **15. Perdita di energia** 0. Ho la stessa energia di sempre. 1. Ho meno energia del solito. 2. Non ho energia sufficiente per fare la maggior parte delle cose. 3. Ho così poca energia che non riesco a fare nulla. **16. Sonno** 0. Non ho notato alcun cambiamento nel mio modo di dormire. 1a. Dormo un po' più del solito. 1b. Dormo un po' meno del solito. 2a. Dormo molto più del solito. 2b. Dormo molto meno del solito. 3a. Dormo quasi tutto il giorno. 3b. Mi sveglio 1-2 ore prima e non riesco a Riaddormentarmi. **17. Irritabilità** 0. Non sono più irritabile del solito. 1. Sono più irritabile del solito. 2. Sono molto più irritabile del solito. Sono sempre irritabile.	2. Ho perso la maggior parte dell'interesse verso le altre persone o cose. 3. Mi risulta difficile interessarmi a qualsiasi cosa. **18. Appetito** 0. Non ho notato alcun cambiamento nel mio appetito. 1a. Il mio appetito è un po' diminuito rispetto al solito. 1b. Il mio appetito è un po' aumentato rispetto al solito 2a. Il mi appetito è molto diminuito rispetto al solito 2b. Il mio appetito è molto aumentato rispetto al solito. 3a. Non ho per niente appetito. 3b. Mangerei in qualsiasi momento **19. Concentrazione** 0. Riesco a concentrarmi come sempre. 1. Non riesco a concentrarmi come al solito. 2. Trovo difficile concentrarmi per molto tempo 3. Non riesco a concentrarmi su nulla. **20. Fatica** 0. Non sono più stanco o affaticato del solito. 1. Mi stanco e mi affatico più facilmente del solito. 2. Sono così stanco e affaticato che non riesco a fare molte delle cose che facevo prima. 3. Sono talmente stanco e affaticato che non riesco più a fare nessuna delle cos e che facevo prima. **21. Sesso** 0a. Non ho notato alcun cambiamento recente nel mio interesse verso il sesso. 0b. Sono meno interessato al sesso rispetto a prima. 1. Ora sono molto meno interessante al sesso. 2. Ho completamente perso l'interesse verso il sesso.

Scoring sommare i punteggi ottenuti ai 21 item (ogni item ha un punteggio da 0 a 3) - le risposte a e b ottengono lo stesso punteggio (ad esempio 1a e 1b valgono sempre 1). Punteggi 0-13 indicano un'assenza di contenuti depressivi; punteggi compresi tra 14-19: una depressione lieve punteggi 27-29 una depressione di grado moderato; punteggi 30- 63: una depressione di grado severo.

Cognitive Reserve Index questionnaire

M. Nucci, D. Mapelli & S. Mondini

Istruzioni: In caso di alterazione cognitiva o comportamentale, anche solo sospetta, il questionario Ł da somministrare ai familiari o a chi si prende cura del paziente, indicandolo al fondo del questionario nella apposita casella.

Cognome: .... Nome: ....

Data di nascita: ....../....../...... Luogo di nascita: .... Età : ....

Luogo di residenza: .... Nazionalit : italiana altro ....

Stato civile: celibe/nubile coniugato divorziato vedovo

CRI - SCUOLA

Istruzioni: Contare gli anni di scuola superati piø 0.5 per gli anni in cui si Ł stati respinti. Per ogni corso di formazione frequentato contare 0.5 ogni 6 mesi.

	Anni
1. Anni di scolarità (compresa eventuale specializzazione)	.....
2. Corsi (0.5 ogni 6 mesi)	.....

CRI - LAVORO

Istruzioni: Indicare gli anni lavorativi approssimati per eccesso, utilizzando una scala di 5 anni in 5 anni (0 - 5 - 10 - 15 - 20 ecc; ad esempio, se una persona ha lavorato per 17 anni, indicare 20). I cinque livelli sono suddivisi per il grado di impegno cognitivo richiesto e di responsabilità personale assunta. Riportare ogni professione esercitata, anche se svolta in contemporanea con altre.

Anni

1. Operaio non specializzato, lavoro in campagna, giardiniere, cameriere, autista, meccanico, idraulico, operatore call center, elettricista ecc.

2. Artigiano o operaio specializzato, impiegato semplice, cuoco, commesso, sarto, infermiere, militare, parrucchiere, rappresentante ecc.

3. Commerciante, impiegato di concetto, religioso, agente di commercio, agente immobiliare, maestra d'asilo, musicista ecc.

4. Dirigente di piccola azienda, libero professionista qualificato, insegnante, imprenditore, medico, avvocato, psicologo, ingegnere ecc.

5. Dirigente di grande azienda, impiego di alta responsabilità ,politico, docente universitario, magistrato, chirurgo, ricercatore, ecc.

Età d'interruzione di ogni attività professionale: .....

CRI - TEMPO LIBERO

Istruzioni:

- Tutte le voci vanno riferite ad attività svolte con regolarità durante la vita adulta (dai 18 anni in seguito).
- Sono escluse tutte le attività che comportino un reddito (in tal caso rifarsi alla sezione IRC - Lavoro).
- Rispondere secondo le frequenze stimate durante il periodo di riferimento (settimanale, mensile, annuale).
- Se le frequenze sono molto cambiate negli anni, rispondere secondo quella piø alta. Ad esempio se una persona ha guidato per circa 30 anni tutti i giorni, ma negli ultimi 15 anni ha guidato solo una due volte alla settimana, allora si risponder Spesso - Sempre .
- Nella colonna Anni riportare per quanti anni l'attività è stata esercitata, approssimando per eccesso e utilizzando una scala di 5 anni in 5 anni (5−10−15−20 ecc.). Ad esempio se una persona ha letto regolarmente un quotidiano per circa 27 anni si riporterà 30 nella colonna degli anni di attività , anche se non legge più da anni.
- La cella indicata con anni è da segnare se la risposta riguarda un'attività ancora attuale e regolarmente esercitata.

1. ATTIVITA' CON FREQUENZA SETTIMANALE

	minore o uguale a 2 volte a settimana	maggiore o uguale a 3 volte a settimana	Anni
1. Lettura di giornali e settimanali	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
2. Attività domestiche (cucinare, lavare, stirare ecc.)	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
3. Guida (escluse biciclette)	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
4. Attività di tempo libero (sport di ogni genere, caccia, ballo, carte, bocce, enigmistica ecc.)	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
5. Uso di nuove tecnologie (macchine digitali, computer, Internet ecc.)	☐ Mai/Di rado	☐ Spesso/Sempre	..... a

2. ATTIVITA' CON FREQUENZA MENSILE

	minore o uguale a 2 volte al mese	maggiore o uguale a 3 volte al mese	Anni
1. Attività sociali (cene con amici, circoli, pro loco, dopolavoro ecc.)	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
2. Cinema o teatro	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
3. Cura dell'orto, giardinaggio, tinta alle pareti, lavori di idraulica, maglia, ricamo ecc.	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
4. Provvedere ai nipoti/ai genitori anziani	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
5. Attività di volontariato	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
6. Attività artistiche (suonare uno strumento, dipingere, scrivere ecc.)	☐ Mai/Di rado	☐ Spesso/Sempre	..... a

3. ATTIVITA' CON FREQUENZA ANNUALE

	minore o uguale a 2 volte all'anno	maggiore o uguale a 3 volte all'anno	Anni
1. Mostre, concerti, conferenze	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
2. Viaggi di più giorni	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
3. Lettura di libri	☐ Mai/Di rado	☐ Spesso/Sempre	..... a

4. ATTIVITA’ CON FREQUENZA FISSA

Istruzioni: Nella Cura dei gli non vanno riportati gli anni di accudimento, la cella indicata con a è da segnare solo quando almeno uno dei figli è minorenne.

			Anni
1. Cura dei figli	☐ No	☐ Sì (numero ......)	a
2. Cura di animali domestici	☐ Mai/Di rado	☐ Spesso/Sempre	..... a
3. Gestione del conto corrente in banca	☐ Mai/Di rado	☐ Spesso/Sempre	..... a

Questionario somministrato: all’interessato all’accompagnatore

Data: ...../...../......

Nome dell’operatore: ....

Risultato

CRI-Scuola ....

CRI-Lavoro ....

CRI-Tempo Libero ....

CRI ....

basso	medio-basso	medio	medio-alto	alto
≤ 70	70 : 85	85 : 115	115 : 130	≥ 130

Digit span test

	Column 1	Column 2
Forward test	(3) 2-6-5	(3) 2-8-1
	(4) 1-5-2-3	(4) 1-9-5-2
	(5) 2-4-7-6-1	(5) 5-2-1-4-3
	(6) 4-2-1-9-3-7	(6) 8-5-3-1-4-7
	(7) 3-6-4-8-5-2-9	(7) 6-8-1-4-7-2-5
	(8) 7-5-8-2-9-6-1-3	(8) 2-8-5-9-7-3-1-4
	(9) 5-8-6-4-2-7-3-9-1	(9) 4-2-5-8-1-3-9-7-6
Backward test	(2) 2-1	(2) 2-8
	(3) 5-8-4	(3) 3-2-8
	(4) 4-8-9-1	(4) 2-9-4-1
	(5) 6-8-7-2-1	(5) 3-5-9-7-6
	(6) 5-8-1-7-4-6	(6) 4-3-1-9-2-5
	(7) 8-5-3-6-7-2-9	(7) 5-3-2-4-1-6-8
	(8) 1-7-4-3-8-9-5-2	(8) 6-8-4-7-5-3-9-2
Maximal digit number for forward test ( ) + Maximal digit number for backward test ( ) = Total score ( )		

Frontal Assessment Battery (FAB)

B Dubois-B Pillon-A Slachevsky-I Litvan

Hôpital del la Salpêtrière, 75013 Paris, France

Sei test da usare al letto del paziente (non richiedono più di 10 minuti)

1. **Somiglianza** (concettualizzazione)
   - *"In che cosa sono simili :*
   - *una banana e un'arancia*

(In caso di fallimento totale: "non sono simili" o di fallimento parziale : "entrambe hanno la buccia", aiutare il paziente : *" la banana e l'arancia sono entrambe ...."*; ma assegnare 0 a questa risposta; non aiutare i paziente per i due successivi item) - *un tavolo e una sedia?*

- *Un tulipano, una rosa e una margherita?"*
- punteggio : solo le risposte categoriali (frutta, mobili, fiori) sono considerate corrette.

3 risposte corrette 3 2 risposte corrette 2 1 risposta corretta 1
nessuna risposta corretta 0

2. **Fluenza fonemica** (flessibilità mentale)
   - *"Dica il maggior numero possibile di parole che cominciano con la lettera "S", qualsiasi parola eccetto cognomi o nomi propri".*

Se il paziente non dà nessuna risposta nei primi 5 secondi, dire : *"Per esempio, serpente"*. Se il paziente si ferma per oltre 10 secondi, stimolarlo dicendo : *"Qualsiasi parola che cominci con la lettera "S"* . La prova dura 60 secondi.

- Punteggio: ripetizioni o variazioni (scarpa, scarpone), cognomi o nomi propri non sono contate come risposte corrette.

Più di 9 parole	3
Da 6 a 9 parole	2
Da 3 a 5 parole	1
Meno di 3 parole	0

3. **Serie Motorie** (programmazione)
   - *"Guardi con attenzione quello che faccio".*

L'esaminatore seduto di fronte al paziente effettua tre volte, da solo, con la mano sinistra la serie di Luria "pugno-taglio-piatto".

- *"Ora faccia lo stesso, con la mano destra prima con me poi da solo".*

L'esaminatore effettua tre volte la stessa serie con il paziente, poi gli dice : *"continui da solo"* - Punteggio:

- il paziente effettua da solo, correttamente, 6 serie consecutive 3

- il paziente effettua da solo, correttamente, almeno 3 serie consecutive 2
- il paziente sbaglia da solo, ma effettua correttamente almeno 3 serie consecutive con l'esaminatore 1
- il paziente non riesce ad effettuare 3 serie consecutive neppure con l'esaminatore. 0

4. **Istruzioni contrastanti** (sensibilità all'interferenza)

- *"Batta due volte quando io batto una volta".*

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove : 1-1-1.

- *"Batta una volta quando io batto due volte".*

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove : 2-2-2.

L'esaminatore effettua la serie seguente : 1-1-2-1-2-2-2-1-1-2. - punteggio :

- nessun errore 3
- 1 o 2 errori 2
- più di 2 errori 1
- il paziente batte come l'esaminatore per almeno 4 prove consecutive 0

5. **Go – No - Go** (controllo inibitorio)

- *"Batta una volta quando io batto una volta".*

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove : 11-1.

- *"Non batta quando io batto due volte".*

Per essere sicuri che il paziente abbia capito le istruzioni, si effettua una serie di tre prove : 22-2-2.

L'esaminatore effettua la serie seguente : 1-1-2-1-2-2-2-1-1-2. - punteggio :

- nessun errore 3
- 1 o 2 errori 2
- più di 2 errori 1
- il paziente batte come l'esaminatore per almeno 4 prove consecutive 0

6. **Comportamento di prensione** (autonomia ambientale)

- L'esaminatore è seduto di fronte al paziente. Mettere le mani del paziente con le palme in alto, appoggiate sulle ginocchia. Senza dire nulla e senza guardare il paziente, l'esaminaotre porte le sue mani vicino a quelle del paziente e ne tocca le palme, contemporaneamente da ambo i lati, osservando se il paziente spontanemaente le afferra. Se il paziente le afferra, l'esaminatore prova di nuovo dopo avergli detto: *"Non prenda le mie mani"* - punteggio :

- il paziente non afferra le mani dell'esaminatore	3
- il paziente e vita o chiede cosa deve fare	2
- il paziente afferra le mani senza esitazione	1
- il paziente afferra le mani dell'esaminatore anche dopo che gli ha chiesto di non farlo	0

TOTALE …../18

Montreal Cognitive Assessment
(MoCA)

7. Istruzioni per la somministrazione e punteggi

Il Montreal Cognitive Assessment (MoCA) è stato progettato come strumento per un rapido screening del deterioramento cognitivo lieve. Valuta diversi domini cognitivi: attenzione e concentrazione, funzioni esecutive, memoria, linguaggio, abilità visuocostruttive, astrazione, calcolo e orientamento. Il tempo di somministrazione del MoCa è di 10 minuti. Il massimo punteggio possibile è 30 punti; un punteggio uguale o superiore a 26 è considerato normale.

1. Trail Making

Istruzioni - L'esaminatore istruisce il soggetto: *"Come vede abbiamo dei numeri crescenti da 1 a 5 e lettere crescenti da A ad E. Per favore, disegni una linea che unisca il primo numero con la prima lettera corrispondente alternando numeri e lettere in ordine crescente e così via. Inizi qui:* (indicare il punto 1) *dal punto "1" e unisca con una linea il punto "1" alla lettera "A" e poi dalla "A" tracci una linea sino al "2" e continui cosi fino alla lettera "E""* (indicare il punto "E").
Punteggio - Assegnare un punto se il soggetto disegna con successo il modello: 1-A-2-B-3-C-4-D-5-E, senza alcun incrocio o sovrapposizione delle linee. Nel caso anche di un solo errore non immediatamente corretto dal soggetto, assegnare zero punti.

2. Abilità visuocostruttive (cubo)

Istruzioni - L'esaminatore dà le seguenti istruzioni, indicando il cubo: *"Copi questo disegno nello spazio sotto e cerchi di farlo il meglio possibile ."*
Punteggio - Assegnare un punto per una corretta esecuzione del disegno.

- Il disegno deve essere tridimensionale
- Tutte le linee devono essere presenti nel disegno
- Non devono essere aggiunte altre linee
- Le linee devono essere relativamente parallele e di lunghezza simile al disegno (prismi rettangolari sono accettati)

Nessun punto viene assegnato se uno qualsiasi dei suddetti criteri non viene rispettato.

3. Abilità visuocostruttive (orologio)

Istruzioni - Indicare lo spazio in alto (terzo a destra) e dare le seguenti istruzioni: "
Disegni un orologio tipo sveglia, un pò grande con tutti i numeri delle ore.

Disegni le lancette in modo che indichino le ore undici e dieci." (Questa seconda parte delle istruzioni può essere ripetuta nel corso della prova dopo che il soggetto ha completato l'inserimento dei numeri nel cerchio.)
Punteggio - Assegnare un punto per ciascuno dei seguenti tre criteri:

- Contorno (1pt): il quadrante deve essere un cerchio regolare e poco distorto (ad esempio : trascurare piccole imperfezioni di chiusura del cerchio).
- Numeri (1pt): tutti i numeri devono essere presenti senza numeri addizionali. Devono essere scritti nell'ordine giusto e posizionati correttamente nei quadranti corrispondenti. I numeri romani sono accettabili; i numeri possono essere disegnati anche fuori dal cerchio.
- Lancette (1pt): ci devono essere due lancette congiunte che indicano l'ora giusta; la lancetta delle ore deve essere chiaramente più corta di quella dei minuti; le lancette devono essere centrate dentro il cerchio dell'orologio e il loro congiungimento deve essere vicino al centro dello stesso.
  Un punto o più non viene assegnato se uno o più dei suddetti criteri non viene rispettato.

4. Denominazione

Istruzioni - Iniziando da sinistra, indicare una figura alla volta , chiedendo: *“Mi dice il nome di questo animale?”*

Punteggio - Assegnare un punto per ciascuna delle seguenti risposte:, (1) leone, (2) rinoceronte, (3) cammello o dromedario.

5. Memoria

Istruzioni - L’esaminatore leggerà un elenco di 5 parole (alla velocità di una al secondo), dopo aver dato le seguenti istruzioni: *“Questa è una prova di memoria. Le leggerò un elenco di parole che lei dovrà ripetere ora e più tardi. Ascolti attentamente. Quando avrò finito, mi dica tutte le parole che riesce a ricordare. Non importa l’ordine in cui le dice.”*
Mettere un segno di conferma nell’apposito spazio per ogni parola che il soggetto pronuncia in questa prima prova.

Quando il soggetto indica che ha finito (ha richiamato tutte le parole), o non riesce a ricordarne altre, leggere l’elenco una seconda volta con le seguenti istruzioni: *“Ora leggerò lo stesso elenco per la seconda volta. Provi a ricordarle e a ripetermi tutte quelle che riesce a ricordare, incluse le parole che ricorda dalla prima prova.”*
Mettere un segno di conferma nell’apposito spazio per ogni parola che il soggetto ricorda dopo la seconda prova.

Alla fine della seconda prova, informare il soggetto che queste parole gli verranno richieste nuovamente, dicendo: *“Io le chiederò di ricordare ancora queste parole fra qualche minuto .”*
Punteggio - Nessun punto è assegnato alla prima e alla seconda prova.

6. Attenzione Digit Span in avanti

Istruzioni - Dare le seguenti indicazioni: *“Le dirò alcuni numeri. Quando avrò finito, li ripeta esattamente come li ho detti.”* La sequenza di cinque cifre dovrà essere scandita al ritmo di una al secondo.

Digit Span all’indietro

Istruzioni - Dare le seguenti indicazioni: *“Ora dirò dei numeri diversi, ma questa volta alla fine, voglio che lei me li ripeta all’indietro.* La sequenza di tre cifre dovrà essere scandita al ritmo di una al secondo. Punteggio - Assegnare un punto ad ogni sequenza ripetuta correttamente (*N.B.:* La risposta giusta nella prova Digit Span all’indietro è 2-4-7).

Attenzione sostenuta

Istruzioni - L’esaminatore leggerà la lista di lettere alla velocità di una al secondo, dopo aver dato le seguenti istruzioni: *“Leggerò una serie di lettere. Ogni volta che dico la lettera A dia un colpetto sul tavolo con la mano. Se dico una lettera differente non dia alcun colpetto.”*
Punteggio - Dare un punto se al massimo è presente un errore (un errore consiste in un colpetto ad una lettera sbagliata o nessun colpetto alla lettera giusta).

Serie di 7

Istruzioni - L’esaminatore dà le seguenti istruzioni: *”Adesso le chiederò di fare una serie di sottrazioni. Cominci a sottrarre 7 da 100, e poi, dal numero che resta, continui a sottrarre 7 finché non le dirò di fermarsi” . Ripetere* queste istruzioni due volte se necessario.
Punteggio - In questa prova si assegnano al massimo 3 punti. Assegnare 0 punti se tutte le sottrazioni vengono sbagliate; assegnare 1 punto se solo 1 sottrazione è corretta, 2 punti per 2 o 3 sottrazioni corrette; 3 punti se il partecipante esegue correttamente 4 o 5 sottrazioni. Contare ogni sottrazione corretta iniziando da 100. Ogni sottrazione è valutata indipendentemente cioè se l’esaminato risponde

con un numero sbagliato ma poi continua a sottrarre correttamente 7 da questo allora assegnare 1 punto per ciascuna sottrazione corretta. Per esempio, uno può rispondere *"92 – 85 – 78 – 71 – 64"* dove il "92" è sbagliato, ma tutti i successivi i numeri sono sottratti correttamente. C'è stato un solo errore e alla prova sarà dato un punteggio di 3.

7. Ripetizione di una frase

Istruzioni - L'esaminatore dà le seguenti indicazioni: *"Le leggerò una frase. La ripeta dopo di me esattamente come la dico (*pausa): ***"So solo che oggi dobbiamo aiutare Giovanni."*** In seguito alla risposta dire: *"Ora le leggerò un'altra frase. La ripeta dopo di me, esattamente come la dico* (pausa): ***"Il gatto si nascondeva sempre sotto il divano quando c'erano cani nella stanza."***
Punteggio - Assegnare 1 punto per ciascuna frase correttamente ripetuta. La ripetizione deve essere esatta. Stare attenti ad errori di omissione (per es. di parole come "solo", "sempre") e di sostituzioni/ aggiunte (per es., "Giovanni è da aiutare oggi", "si nasconde" invece di "si nascondeva", plurali alterati, ecc.).

8. Fluenza

Istruzioni - L'esaminatore dà le seguenti indicazioni: *"Mi dica tutte le parole che le vengono in mente che iniziano con una certa lettera dell'alfabeto che le dirò tra poco. Lei può dirmi qualsiasi tipo di parola tranne i nomi propri (come Barbara o Bologna), i numeri o parole che hanno la stessa radice, per es. amore, amante* e *amoroso. Le dirò io di fermarsi dopo un minuto. È pronto?* (pausa) *Ora mi dica tutte le parole che le vengono in mente che iniziano con la lettera F .* (dopo 60 sec.) *Stop, si fermi."*
Punteggio - Assegnare un punto se il soggetto pronuncia 11 o più parole in 60 sec. Registrare le risposte del soggetto in basso o sul margine a fianco.

9. Astrazione

Istruzioni - L'esaminatore chiede al soggetto di spiegare cosa hanno in comune ogni coppia di parole, cominciando con l'esempio: *Può dirmi in che cosa sono simili l'arancia e la banana?* Se il soggetto risponde in maniera concreta, cioè indicando caratteristiche non astratte, allora ripetere una sola volta: *"Mi dice in che altro modo sono simili."* Se il soggetto non dà la risposta adeguata (*frutti*), dire: *"Si, esatto, e sono anche entrambi frutti."* Non aggiungere altre istruzioni o altri chiarimenti.

Dopo questo esercizio di prova, dire: *"Ora, mi dica in che cosa sono simili il treno e la bicicletta?"* segnare la risposta e proseguire chiedendo: *"Ora, mi dica in che cosa sono simili un righello e un orologio ?"* Non aggiungere altre istruzioni o altri suggerimenti.

Punteggio - Vengono tenute in considerazione solo le ultime due coppie. Assegnare un punto ad ogni risposta giusta.

Le seguenti risposte sono considerate accettabili:

Treno – bicicletta = mezzi di trasporto, mezzi con cui viaggiare, si possono fare piccoli viaggi con entrambi.

Righello – orologio = strumenti di misura, usati per misurare.

Le seguenti risposte **non** sono accettabili:

Treno – bicicletta = hanno le ruote; Righello – orologio = hanno i numeri.

10. Richiamo differito

Istruzioni - L'esaminatore dà le seguenti indicazioni: *"Prima le ho letto alcune parole che le avevo chiesto di tenere in mente. Adesso mi dica tutte le parole che riesce a ricordare."* Mettere un segno di conferma nell'apposito spazio, per ciascuna delle parole correttamente ricordate in modo spontaneo, senza alcun aiuto.

Punteggio- **Assegnare un punto per ogni parola ricordata spontaneamente, senza alcun aiuto.**

Opzionale:

Al termine di questa prova, per ogni parola non ricordata, stimolare il soggetto con l'aiuto del suggerimento contenuto nelle rispettive categorie semantiche indicate sotto. Se il soggetto non ricorda delle parole anche dopo lo stimolo fornito dalle rispettive categorie semantiche allora passare subito alla rispettiva modalità di risposta a scelta multipla fornendo le seguenti istruzioni : (ad es.) *"Quale delle seguenti parole pensa che fosse quella giusta, NASO, FACCIA o MANO?"*

Mettere un segno di conferma (√) nell'apposito spazio a seconda che il soggetto sia riuscito a ricordare correttamente la parola con l'aiuto della categorie semantica o della risposta a scelta multipla.

	Tipo di aiuto		**Tipo di aiuto**	
Faccia	categoria semantica	parte del corpo	risposta a scelta multipla ___	naso, faccia, mano
Velluto	categoria semantica	tipo di tessuto	risposta a scelta multipla ___	lana, cotone, velluto
Chiesa	categoria semantica	tipo di edificio	risposta a scelta multipla ___	chiesa, scuola, ospedale
Margherita	categoria semantica	tipo di fiore	risposta a scelta multipla ___	rosa, margherita, tulipano
Rosso	categoria semantica	un colore	risposta a scelta multipla ___	rosso, blu, verde

Punteggio - **Nessun punto è assegnato per le parole ricordate con un aiuto.** L'aiuto è usato solo a scopo clinico per ottenere informazioni e può fornire interpretazioni aggiuntive riguardanti il tipo di disturbo mnesico. Per deficit della memoria dovuti a errori nel richiamo, la prestazione può essere migliorata con un aiuto. Per deficit della memoria dovuti a difficoltà o incapacità nella codificazione, la prestazione non può essere migliorata con un aiuto.

11. Orientamento

Istruzioni - L'esaminatore dà le seguenti indicazioni: *"Mi dica la data di oggi, completa di anno ".* Se il soggetto non fornisce una risposta completa, allora aiutarlo dicendo: *"mi dica* [*l'anno, il mese, la data esatta e il giorno della settimana*]*".* Poi chiedere: *"Ora mi dica il nome di questo posto e in quale città si trova".*

Punteggio - Dare un punto a ciascuna risposta giusta. Il soggetto deve dire la data esatta e il nome preciso del luogo (nome dell'ospedale, casa protetta, clinica, ambulatorio, abitazione, ecc.…).

N.B. Assegnare 0 punti se il soggetto sbaglia anche di un solo giorno (+ o -) la data più il giorno della settimana.

Risultato totale - Sommare tutti i risultati delle singole prove elencati nella colonna destra del foglio.

Aggiungere un punto se la persona ha 12 o meno anni d'istruzione. Il massimo punteggio è di 30 punti. Un punteggio totale uguale o superiore a 26 è considerato normale

Mini Mental State Evaluation (M.M.S.E.)

Test somministrabile ………………. |_| si |_| no

In che anno siamo? (0-1)____|________

In che stagione siamo? (0-1)____|________

In che mese siamo? (0-1)____|________

Mi dica la data di oggi (0-1)____|________

Che giorno della settimana è oggi? (0-1)____|________

Mi dica in che Nazione siamo? (0-1)____|_______

Mi dica in che Regione ci troviamo? (0-1)____|_______

In che città siamo? (0-1)____|_______

In che edificio ci troviamo? (0-1)____|_______

A che piano siamo? (0-1)____|_______

Far ripetere: "pane, casa, gatto". La prima ripetizione dà adito al punteggio.

1.________________ 2.__________________ 3.__________________ |_______

Ripetere finché il soggetto esegue correttamente, max 6 volte (0-3)

Far contare a ritroso da 100 togliendo 7 per cinque volte:

93 86 79 72 65 (|_______

Se non completa questa prova, allora far sillabare all'indietro la parola:

MONDO: O- D - N - O - M - (0-5) |_______

Chiedere la ripetizione dei tre soggetti precedenti (0-3)

1.________________ 2.__________________ 3.__________________ |______

Mostrare un orologio ed una matita chiedendo di dirne il nome (0-2)________________________|_______

Ripeta questa frase "tigre contro tigre" (0-1)____|______

Prenda questo foglio con la mano destra, lo pieghi e lo metta sul tavolo (0-3)__________________|______

Scriva una frase (deve ottenere soggetto e verbo) (0-1)____________________________________|_____

Copi questo disegno (pentagoni intrecciati)* (0-1)____|______

Punteggio Totale ………………… ____________

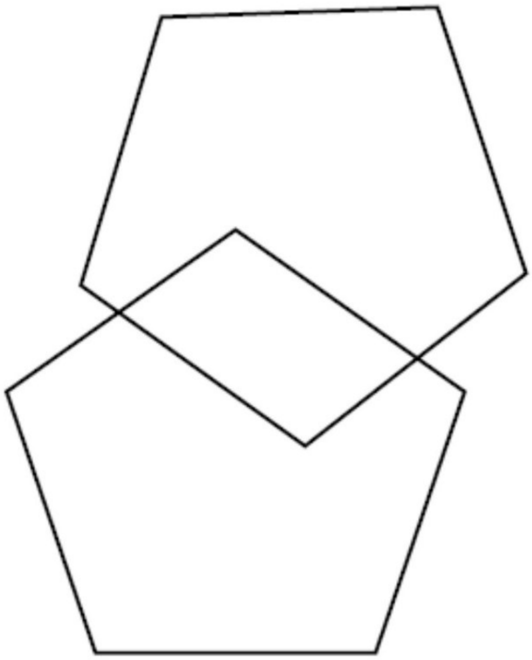
Punteggio totale corretto per età e scolarità**... ____________

**Coefficienti di aggiustamento del MMSE per classi di età ed educazione della popolazione italiana

Intervallo di età	**65 - 69**	**70 -74**	**75 – 79**	**80 – 84**	**85 – 89**
Anni di Scolarizzazione					
0 – 4 anni	**+0,4**	**+0,7**	**+1,0**	**+1,5**	**+2,2**
5 – 7 anni	-1,1	-0,7	-0,3	+0,4	+1,4
8 – 12 anni	**-2,0**	**-1,6**	**-1,0**	**-0,3**	**+0,8**
13 – 17 anni	-2,8	-2,3	-1,7	-0,9	+0,3

Il coefficiente va aggiunto (o sottratto) al punteggio grezzo del MMSE per ottenere il punteggio aggiustato

*Disegno



C H I U D A

G L I

O C C H I