New frontiers in neuropsychology.

The Padua Rehabilitation Tool: a new software for rehabilitation using touch-screen technology

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Summary

Recently, the advancement and the development of new technologies is shaping and establishing new frontiers in neuropsychological rehabilitation. In particular, the use of touchscreen technology, together with the use of mobile devices, is giving new opportunities for the development of innovative programs of rehabilitation tailored to the specific needs of patients. The touchscreen technology allows to go beyond some limits of classic paper and pencil exercise including the possibility for patients of practice rehabilitation outside clinic in a personalized manner and controlled by remote by the clinician. The overview of software for rehabilitation today is wide, but the poor availability of such software for Italian population and specifically designed for people with cognitive impairments, some years ago, led me to the development of the first mobile devices' software for cognitive rehabilitation. The aim of this dissertation is to describe the development process and the efficacy evaluation of this software, the Padua Rehabilitation Tool (PRT).

Initially will be described and analyzed the base for every cognitive intervention: the plasticity of brain. Today, we know that the brain has the ability to undergo functional and structural alterations in response to internal and external environmental changes, including cognitive interventions. Moreover, I will discuss the use of technology and computerized training for rehabilitation. In Section1 I will report a study for understanding the relationship between performance in computerized exercises and the performance in standardized tests. None before investigated the relationship between this two different measures of outcome. The perceived relationship is not necessarily automatically provided, thus, it is important to examine how exercises and standardized tests are related: if improvement in therapy exercises mirrors improvement in standardized test. The results of this study will confirm that changes in performance on therapy exercises and in standardized test are not just in co-occurrence but are directly related each other and this relation allows the clinician to make predictions.

In Section 2, I will describe the development of the PRT and the use of this software in population with different etiologies. Originally, the PRT was designed for people with dementia and thus the most important study of efficacy was conducted on this population. I will report the results of a comparison between a cognitive training using PRT, a classic paper and pencil training, and a no treatment condition. It is demonstrated that both cognitive interventions led to significantly improvement compared to no treatment conditions. Moreover, the cognitive training using the Padua Rehabilitation Tool is effective such as a more classic paper and pencil approach to rehabilitation. Thus, the advantages of using touch screen technology rely on usability, portability, precision and motivation aspects rather than in efficacy.

Lastly, given the flexibility and the variety of exercises and cognitive domains engaged by the PRT it was possible to deliver a cognitive rehabilitation to people with acquired brain injury. I will describe the effects of a cognitive rehabilitation with PRT in several single cases including patients after stroke, with a history of traumatic brain injury and an early post-coma rehabilitation. The results obtained with these patients were certainly positive, and in most of the cases, the cognitive improvement was observed also in the neuropsychological assessment.

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General Introduction

Chapter_1 Basis of Neuropsychological Rehabilitation: The Plastic Brain

Over the past quarter of a century there have been interest in the long-term impact of acquired brain injury (ABI). Thanks to an increased interest in understanding the underlying mechanisms of injury, as well as the nature of acquired physical, cognitive, behavioral, and emotional consequences of such injuries, today is possible to develop more accurate treatment for individuals with acquired brain injury. Precise models of cognitive functioning allow to program specific treatment for patients with different etiologies and different deficits. From a general definition of *cognitive rehabilitation* that focus too heavily on remediating or compensating for decreased cognitive abilities we are now moving to the term of *rehabilitation of individuals with cognitive impairment* that probably better captures the emphasis on brain injured individuals that has and will always be the target of cognitive rehabilitation (Sohlberg & Mateer, 2001). Although some of the fundamental goals of improving and compensating for cognitive abilities continue to be mainstays of rehabilitation efforts we can describe two mayor forces that are shaping cognitive rehabilitation towards new perspectives of treatment: new findings with regard to **neuroplasticity** and the advances in **technology**. The focus of this first chapter is on the description of neuroplasticity.

The notion of neuroplasticity is particularly relevant to rehabilitation and thanks to neuroscience there is no doubt that the brain is fundamentally altered by experience. Presently, we know that the brain is a far more plastic organ than was long thought before and it is capable of considerable reorganization that can form the basis of recovery. In this chapter are reviewed the different mechanism of plasticity and it will be described cortical reorganization reporting studies on both animal and human brain.

1.1.   Mechanisms underlying brain plasticity

Several mechanisms underlying brain plasticity have been described and suggested (Duffau, 2006; Huang & Chen, 2015). One of these is the *neurogenesis*: it has been long assumed that the production of new neurons occurs only during development and stops before puberty (Cajal & May, 1991; Kölliker, 1867). Gross (2000) describes the decline in the belief of this dogma and the general paradigm shift that recognizes the plasticity of the adult brain and its structural modulation by experience. Adult neurogenesis was shown in the dentate gyrus of the marmoset and macaque (Gould et al., 1999; Gould, Tanapat, McEwen, Flügge, & Fuchs, 1998), in rats (Cameron & Mckay, 2001; Gage et al., 1995), and in humans (Eriksson et al., 1998; Roy et al., 2000). Considering that a higher density of new neurons is generated in the hippocampus is possible that neurogenesis in mammals has an important role for learning and memory. As speculated by Gross (2000) these new neurons may be related to the formation of memories and in particular the daily addition of neurons to the

brain may account for the fact that long-term memories are time-tagged, as suggested by aspects of memory loss in human patients. For example, in the recovery from traumatic amnesia, the oldest memories return first. Moreover, in conditions such as Alzheimer's disease, there is a progressive retrograde loss of more remote memories. These temporal gradients imply that younger memories are different from older ones, in the sense that older memories are more resistant to interference by trauma and disease. The neurogenesis in anatomical area related to memories, such as hippocampus, suggests a possible mechanism for this phenomenon. There may be sets of cells that store a particular memory, with new adult-generated neurons continually added to such memory circuits. Therefore, the older the circuit for a particular memory, the more neurons it would have and the more resistant it might be to trauma because of greater redundancy, greater spatial dispersion or both. Such a scheme may account for the greater resistance of older memories to loss of (or interference with) retrieval. *Neurogenesis* could also be involved in post-lesional plasticity: for example, experimental evidences support the idea that the stroke-damaged adult brain makes an attempt to repair itself by producing new neurons also in areas where neurogenesis does not normally occur (Arvidsson, Collin, Kirik, Kokaia, & Lindvall, 2002; Lindvall & Kokaia, 2015; Magnusson et al., 2014; Thored et al., 2006).

Another different mechanism underlying plasticity is the *unmasking* of latent connections and networks underlining the important role of the modulation of GABAergic inhibition (Chen, Cohen, & Hallett, 2002). GABA is the most important inhibitory neurotransmitter in the brain (Jones, 1993): normally, it blocks horizontal connections between pyramidal cells. However, if these inhibitor effect is suppressed, these intra-cortical connections become functional transforming silent synapses to functional synapses. This unmasking represents a mayor mechanism of short-term plasticity (Blitz, Foster, & Regehr, 2004; Malenka & Nicoll, 1997; Rioult-Pedotti, Friedman, Hess, & Donoghue, 1998).

Furthermore, several structure modifications in neurons have been described: dendritic spine and axonal sprouting have been observed in vitro and in animals (Lamprecht & LeDoux, 2004). Changes in shape and size of dendritic spines and the attendant redistribution of post-synaptic receptors in their membrane is subject to a continuous regulation (Berlucchi, 2011): the experience drives the formation and elimination of synapses, remodeling the neural circuits (Trachtenberg et al., 2002). Furthermore, rapid structural changes in number, size and shape of dendritic spines have been observed rapidly after damage (Carmichael, 2006; Maletic-Savatic, Malinow, & Svoboda, 1999). This changes are facilitated by a reduction in a major class of growth-inhibitory proteins and an increase in growth-promoting molecules (Carmichael et al., 2005; Carmichael, Wei, Rovainen, & Woolsey, 2001). The neurotrophins, the molecules that control the differentiation and survival of neurons, are also known to be involved in the modulation of synaptic transmission. The enlargement of dendritic spines

associated with long-term potentiation relies on activity-dependent protein synthesis as well as on the action of the brain-derived neurotrophic factor (BDNF) (Tanaka et al., 2008). BDNF plays multiple roles in neuroplasticity and the BDNF-mediated actions are very diverse and range in a time scale from milliseconds to hours (Leal, Afonso, Salazar, & Duarte, 2015). Short-term effects of BDNF include alterations in synaptic properties, such as modulation of neurotransmitter release. The neurotrophin also acts within minutes to alter synapse structure and composition, or within hours to induce long-lasting synaptic changes that depend on BDNF-induced protein synthesis and gene expression (Leal, Comprido, & Duarte, 2014; Lu, Christian, & Lu, 2008; Park & Poo, 2013; Zagrebelsky & Korte, 2014).

1.2.   Cortical reorganization: peripheral lesion

The neuroplasticity was initially described as *cortical reorganization* in response to peripheral lesion. Firstly, Devor and Wall (1981) reported significant changes in the spinal cord of adult rats after an injury to the periphery nerves. Subsequently, reorganization in adult primary sensory cortices has also been demonstrated, including the primary auditory cortex in response to restricted cochlear lesions (Rajan, Irvine, Wise, & Heil, 1993; Robertson & Irvine, 1989), the primary visual cortex in response to lesions on the retina (Eysel et al., 1999; Giannikopoulos & Eysel, 2006; Heinen & Skavenski, 1991; Kaas et al., 1990; Schmid, Rosa, Calford, & Ambler, 1996) and the somatosensory cortex in response to deafferentation of sensory input from a skin area (Merzenich et al., 1984; Merzenich, Kaas, Wall, Nelson, et al., 1983; Merzenich, Kaas, Wall, Sur, et al., 1983; Pons et al., 1991; Rasmusson, 1982; Weiss, Miltner, Liepert, Meissner, & Taub, 2004). In all these studies were reported comparable effects in the relevant cortical regions induced by a lesion: the cortical territory devoted to representing the deafferented region on the sensory surface (the skin, the cochlea, or the retina) becomes responsive to adjacent sensory surfaces spared from the lesion. For example, Calford and Tweedale (1988) described the changes in response in the primary somatosensory cortex in flying-fox following amputation of the single exposed digit on the forelimb. They reported how, immediately after amputation, neurons in the cortex receiving input from the missing digit were not silent but were responding to stimulation to adjoined regions of the digit, hand, harm, and wing. In the week following the amputation this enlarged receptive fields shrank covering only the skin around the amputation.

While these studies were conducted on animals, similar mechanisms of cortical reorganization are observed and described in patients with phantom limb pain: the subjective experience where a person continues to feel pain with his amputated limb as if it were still attached to the body. This phenomenon suggests a cortical reorganization after the amputation of the limb (Cohen, Bandinelli, Findley, & Hallett, 1991; Elbert et al., 1997). A lot of studies described how the cortical maps of the removed

limb in the postcentral gyrus (i.e., primary somatosensory cortex, S1) have been engaged with the area around them (Birbaumer et al., 1997; Flor et al., 1995; Lotze, Flor, Grodd, Larbig, & Birbaumer, 2001; Montoya et al., 1998; Ramachandran & Rogers-Ramachandran, 2000; Ramachandran, Stewart, & Rogers-Ramachandran, 1992). This studies showed that touching different parts of the face led to the tactile sensations at different parts of the missing limb of amputees, and the perception of touch and pain were the perceptual correlate of cortical reorganization in the brain. Recently, other studies showed that the adult brain is capable of altering neuronal responses to adapt to novel environments following loss of peripheral input (Abe et al., 2015; Botelho, Ceriatte, Soares, Gattass, & Fiorani, 2014; Marik, Yamahachi, Meyer zum Alten Borgloh, & Gilbert, 2014; Sammons & Keck, 2015; Simoes et al., 2012).

1.3. Cortical reorganization: cortical lesion

Other studies examined the mechanism of cortical reorganization in response to cortical lesion. The Central Nervous System has the ability to partially recover the ability lost because of a lesion through a reorganization of the spared tissue. It is possible to describe three different process: (1) if the lesion is partial, the recovery of the function is mediated by the reorganization of the undamaged tissue and the perilesional area; if the lesion involves all the region responsible for a specific function, (2) we assist to an activation of secondary areas in the same hemisphere allowing for a partial recover of the function, or (3) an activation of homologous regions in the undamaged hemisphere. Early in 20th century Leyton and Sherington (1917) described the effects of ablation of the arm area in chimpanzees. They firstly identified the M1 arm area using surface stimulation techniques and then excised the area yielding movements of thumb, fingers, wrist, and elbow. Significant paresis was observed in the hand contralateral to the lesion during the initial week after the lesion. However, after 1 month, significant recovery of movement was observed in the affected hand. Similarly, Gless and Cole (1950) reported that after ablating the thumb area of primary motor cortex, the thumb representation reappeared in the adjacent, intact motor cortex. Post-injury reorganization has also been observed in somatosensory cortex: following a small infarct in the primary somatosensory (area 3b) hand representation in monkeys, the injured digit representations reemerge in adjacent, intact tissue (Jenkins & Merzenich, 1987). Moreover, representations of the affected digits expand in other somatosensory areas, such as areas 3a and 1 (Xerri, Merzenich, Peterson, & Jenkins, 1998). Several noninvasive techniques have been used in humans examining the effects of cortical injury on the function of intact cortical tissue: peri-lesional changes in cortical activity have been shown to occur using magnetoencephalography and proton magnetic resonance spectroscopy (Kamada et al., 1997), transcranial magnetic stimulation (Classen et al., 1997), functional magnetic resonance imaging (Cramer et al., 1997) and positron emission tomography (Seitz et al., 1995). It has also been shown

that, after recovery, movement of the recovered hand was associated with increased bilateral activation of remote brain areas, such as the cerebellum, and premotor cortex, as well as the sensorimotor cortex. Interestingly, these increased activations often have occurred in the sensorimotor cortex of the uninjured hemisphere after good recovery, leading many to speculate that the uninjured hemisphere plays a significant role in recovery (Cao, D'Olhaberriague, Vikingstad, Levine, & Welch, 1998; Nelles et al., 1999; Seitz et al., 1998). Although increased activity in undamaged hemisphere may contribute to some of the compensatory gains, it may also be exerting an inhibitory effect on the damaged hemisphere that reduces the potential recovery of its damaged circuits. Indeed, sometimes paradoxical improvements in performance occur after a second lesion on the opposite side of the brain: a patient with marked left-sided neglect following a right-hemisphere stroke, had a resolution of the neglect following a left-hemisphere stroke several months later. Perhaps this occurred because the new lesion reduced the activity of left-sided neural networks that were excessively inhibiting the originally damaged right-hemisphere circuitry. The role of the undamaged hemisphere is still debated to establish whether the right hemisphere recruitment facilitates or impedes recovery from aphasia. Some functional imaging studies have supported the evidence that right hemisphere can reorganize in order to assume functions of the left hemisphere (Blasi et al., 2002; Leff et al., 2002; Musso et al., 1999; Saur et al., 2006) although the right hemisphere is computationally less efficient in its language processing than native left hemisphere areas (Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Heiss, Thiel, Kessler, & Herholz, 2003; Winhuisen et al., 2005). Other studies, instead, reported that right hemisphere is ineffective suggesting that contralesional areas play a dysfunctional role rather than compensatory: over-activity in right hemisphere areas inhibits recovery of left hemisphere perilesional cortex, limiting recovery from aphasia (Postman-Caucheteux et al., 2010; M. Richter, Miltner, & Straube, 2008). This "theory of interhemispheric inhibition" has motivated several studies attempting to use inhibitory right hemisphere transcranial magnetic stimulation (TMS) as a treatment to improve aphasia (Turkeltaub, 2015). The most consistent effect of right hemisphere TMS has sustained improvement in speech production after inhibition of the right inferior frontal gyrus (pars triangularis) (Barwood et al., 2011; Hamilton et al., 2010; Martin et al., 2009; Naeser et al., 2005). This beneficial effect of inhibitory on aphasia recovery has been taken as evidence that right hemisphere recruitment is detrimental to recovery.

1.4.   Cortical reorganization: exposure to environment and learning

So far, most of the discussed studies examined plasticity as result of a central or peripheral lesion. Other studies investigated the mechanism of *cortical reorganization* as results of exposure to an environment or as effects of learning. Numerous studies examined the effects of an enriched

environment on rats (Bennett, Rosenzweig, & Diamond, 1969; Bennett, Rosenzweig, Diamond, Morimoto, & Hebert, 1974; Rosenzweig, Krech, Bennett, & Diamond, 1962). In the enriched environment condition (EC) rats are placed in large cages containing some stimulus objects such as balls, running wheels, tunnels, and ladders. In contrast to this environmental complexity the impoverished environment condition (IC) consisted of housing the animals singly in small cages. In between these two environmental conditions a standard environment (SC) consists of housing rats in laboratory group cages. Results shown that animals in the enriched condition had more glial cells, increased size of neuronal soma and increased number of dendritic spines. Regarding the effects of learning it has been shown in studies with owl monkeys that a prolonged increase of tactile stimulation to the distal pad of one or two phalanges results in a greatly increased cortical representation specific to that portion of the fingers. Moreover, the effects of increased topography, increased representations of the trained skin location, increased receptive-field size and increased receptive-field overlap were not observed in the representation of the untrained hands in these same monkeys (Jenkins, Merzenich, Ochs, Allard, & Guíc-Robles, 1990; Recanzone et al., 1992). Evidence has also been reported that suggests mechanisms of *cortical reorganization* due to learning and experience in humans. There is growing evidence that musical expertise has profound consequences on the anatomo-functional organization of the human brain (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Gaab, Gaser, & Schlaug, 2006; Martin et al., 2009; Münte, Altenmüller, & Jäncke, 2002; Pantev et al., 2003; Pantev, Engelien, Candia, & Elbert, 2001). Moreno et al. (2009) conducted a longitudinal study with 32 non-musician children to determine whether functional differences between musician and non-musician children reflect specific predispositions for music or result from musical training and whether musical training improves nonmusical brain functions such as reading and linguistic pitch processing. They recorded event-related brain potentials while 8-year-old children performed tasks designed to test the hypothesis that musical training improves pitch processing not only in music but also in speech. Following the first testing sessions non-musician children were pseudorandomly assigned to music or to painting training for 6 months and were tested again after training using the same tests. After musical but not painting training, children showed enhanced reading and pitch discrimination abilities in speech. Remarkably, 6 months of musical training thus suffices to significantly improve behavior and to influence the development of neural processes as reflected in specific pattern of brain waves. These results reveal positive transfer from music to speech and highlight the influence of musical training. Also, they demonstrate brain plasticity in showing that relatively short periods of training have strong consequences on the functional organization of the children's brain. Other evidence of plasticity comes from the study of Pascual-Leone and Torres (1993). They studied the organization of the somatosensory cortex in proficient Braille readers,

recording somatosensory evoked potentials and comparing the results with those of 15 control subjects. The results suggest that reading Braille is associated with expansion of the sensorimotor cortical representation of the reading finger in Braille readers compared with the representation of their left index (non-reading) finger and the right and left index fingers representations of the control subjects. Another classic study that supports the evidence of the capacity for local plastic change in the structure of the healthy adult human brain in response to environmental demands was conducted on licensed London taxi drivers (Maguire et al., 2000). Taxi drivers in London must undergo extensive training - which takes about 2 years to acquire on average - learning how to navigate between thousands of places in the city. Moreover, to be licensed to operate, they have to pass a very stringent set of police examinations. Therefore, London taxi drivers are ideally suited for the study of the direct effect of spatial experience on brain structure. In their study Maguire and colleagues analyzed structural MRIs of the brains of licensed London taxi drivers and compared with those of control subjects who did not drive taxis. Results showed how the posterior and anterior hippocampi of taxi drivers were significantly larger relative to those of control subjects. Moreover, hippocampal volume correlates with the amount of time spent as a taxi driver - positively in the posterior and negatively in the anterior hippocampus. These data are in accordance with the idea that the posterior hippocampus stores a spatial representation of the environment and can expand regionally to accommodate elaboration of this representation in people with a high dependence on navigational skills. Another growing body of studies about experience-dependent changes in brain structure are related to the bi- or multilingualism. Two different reviews examined the structural brain changes related to bilingualism (P. Li, Legault, & Litcofsky, 2014; Stein, Winkler, Kaiser, & Dierks, 2014). Aggregating the existing evidence, the Authors conclude that structural changes in left inferior frontal and inferior parietal regions have been observed in studies on cortical gray matter changes (Klein, Mok, Chen, & Watkins, 2014; Mechelli et al., 2004), while the anterior parts of the corpus callosum have been repeatedly found to reflect bilingualism in studies on white matter connectivity (García-Pentón, Pérez Fernández, Iturria-Medina, Gillon-Dowens, & Carreiras, 2014; Mohades et al., 2012; Pliatsikas, Moschopoulou, & Saddy, 2015).

Other evidence on experience-dependent structural plasticity comes from studies (1) on jugglers, suggesting how training the perception and spatial anticipation of moving objects is a strong stimulus for structural plasticity in the visual areas, used for the retention of visual-motion information (Draganski et al., 2004); (2) on basketball players suggesting the effect of extensive practice and performance of sports-related motor skills on vermian lobules in cerebellum (I. S. Park et al., 2009); (3) on mathematicians, suggesting the effects of long-term practices of visuospatial and arithmetic data processing on cortical gray matter density in the bilateral inferior parietal lobules and left inferior

frontal gyrus (Aydin et al., 2007); (4) on "Baduk" players, suggesting the effects of long training in complex cognitive processes that include spatial perception, attention, working memory, executive control, and problem solving on the fronto–cingulo–striato–thalamic connectivity (Lee et al., 2010). (5) on golf players, suggesting the effect of training in a sensorimotor control task during which a movement has to be aligned according to an external goal on left dorsal premotor cortex, left posterior parietal cortex and right pre-dorsal motor cortex (Jäncke, Koeneke, Hoppe, Rominger, & Hänggi, 2009).

1.5.　Cortical reorganization: effects of cognitive training

Finally, once is well established that the human brain is a plastic organ experience-dependent and it is capable of reorganization, could be interesting to report studies that described whether the mechanisms of *cortical reorganization* described above occur also as consequence of a cognitive training or rehabilitation and whether they occur in the elderly people: understanding the biological basis of cognitive rehabilitation is essential to maximize treatment efficacy. Unfortunately, there is limited research relating cognitive rehabilitation to basic neurobiological principles of recovery and mechanisms of plasticity. In their study Laatsch et colleagues (2004) used functional magnetic resonance imaging (fMRI) to demonstrate brain plasticity in response to cognitive rehabilitation following mild traumatic brain injury in 5 subjects. They discussed changes in fMRI activation for each subject and then related to changes on neuropsychological measures, demonstrating how fMRI can illustrate the neurobiological mechanisms of recovery in individual subjects. As example one patient was a young, right-handed woman who was seen 29-month post-traumatic brain injury resulting from an accident with a truck while riding a bicycle. While neuropsychological tests of language fluency and visual scanning were within the average and low-average range, her past educational performance and occupation suggested that these scores were below prior capabilities. Moreover, she was continuing to complain concerning word finding, reading and visual processing while teaching and coaching. The rehabilitation program continued for 1 year and focused on oral reading, word finding exercises, visual scanning, visual spatial perception and reading speed. Post-treatment fMRI demonstrated increases in the number of activated voxels on all tasks, a bilateral activation of both Broca's and Wernicke's areas with greater activation in the left language areas, and an increased involvement in the intraparietal area, cerebellum and both frontal and supplemental eye. Different pattern where observed in the other patients and the Authors concluded assuming that the variability in subject responses to cognitive rehabilitation supports the notion of tailoring rehabilitation strategies to each subject in order to optimize recovery following brain injury.

A single case study conducted by DeGutis, Bentin, Robertson and D'Esposito (2007) shows the effects of an extensive training for a prosopagnosic patient. They used fMRI and

electroencephalography (EEG) to measure neural changes associated with training configural processing in congenital prosopagnosia. Event-related potential results revealed that although the N170 was not selective for faces before training, its selectivity after training was normal. fMRI demonstrated increased functional connectivity between ventral occipital temporal face-selective regions (right occipital face area and right fusiform face area) that accompanied improvement in face recognition. Several other regions showed fMRI activity changes with training; the majority of these regions increased connectivity with face-selective regions. Together, the neural mechanisms associated with face recognition improvements involved strengthening early face-selective mechanisms and increased coordination between face-selective and non-selective regions, particularly in the right hemisphere.

In another single case study Small, Flores and Noll (1998), used fMRI to study cortical reorganization in a right handed patient with an acquired reading disorder from stroke, unable to read nonwords and with a poor reading of function words. Following therapy, she was able to read nonwords and function words. fMRI was performed during a reading task before and after treatment: prior to therapy, her main focus of brain activation was in the left angular gyrus (area 39) while after therapy it was in the left lingual gyrus (area 18).

Takeuchi et al. (2010) investigated the impact of a training of working memory in healthy individuals through voxel-based analysis (VBA) of fractional anisotropy (FA) using diffusion tensor imaging (DTI) of white matter connectivity changes. DTI is used to measure the magnitude and direction of water diffusion (i.e., anisotropy) in brain tissue and FA is thought to be modulated by the degree of myelination, axonal membrane thickness and diameter, and/or the amount of parallel organization of the axons. The working memory training was associated with FA increases in the white matter region close to the infero-parietal sulcus, which connects working memory nodes, and it was associated with increases of white matter structural integrity in the white matter adjacent to the anterior part of the body of the corpus callosum, which connects the bilateral dorsolateral prefrontal cortexes, the key nodes of working memory.

Other evidences of plasticity following a specific treatment comes from the study that investigated the mechanisms of recovery from aphasia (Cornelissen et al., 2003; Fridriksson, Richardson, Fillmore, & Cai, 2012; Marcotte, Perlbarg, Marrelec, Benali, & Ansaldo, 2013; Rochon et al., 2010; Van Hees et al., 2014; Vitali et al., 2010). For example, Meinzer et al. (2008) discussed the effect of a 10-day intensive language training in patient with a chronic state of aphasia: language improvement for trained materials was significantly related to increased functional activity (fMRI) within areas of excessive slow wave activity suggesting that improvement was mediated by reintegration of, or increased connectivity within, these perilesional areas. Moreover, they didn't find a correlation for

the untrained materials, even though there was also, but less pronounced, improvement for these items. Further studies investigated the neural correlation of generalization effect of treatment in aphasia. Sandberg, Bohland and Kiran (2015) described the changes in functional connectivity related to direct training and generalization effects of a word finding treatment in chronic aphasia. The direct training effects coincided with an increased functional connectivity in the abstract word network, specifically left inferior frontal gyrus, left superior temporal gyrus, and left middle temporal gyrus. The generalization effects coincided with an increased functional connectivity in the concrete difference network, with the highest node degree in the left medial superior frontal gyrus and the right inferior frontal gyrus.

Other important evidences comes from Kim et al. (2009) which investigated the plasticity of the attentional network after a cognitive training in patients with traumatic brain injury. They aimed to delineate the cerebral attentional network in patients with traumatic brain injury and assess for adaptations in this network in response to a rehabilitation intervention. Seventeen patients with TBI and 15 healthy subjects underwent functional magnetic resonance imaging (fMRI) using a visuospatial attention task. Ten TBI patients who successfully completed attentional training had a follow-up fMRI. In the TBI patients, fMRI analysis showed more activation in the frontal and temporo-parietal lobes, as well as less activation in the anterior cingulated gyrus, supplementary motor cortex, and temporooccipital regions compared to the healthy subjects. Following cognitive training, the TBI patients improved performance of attention tasks accompanied by changes in attentional network activation: the activity of the frontal lobe decreased, whereas activation of the anterior cingulate cortices and precuneus increased.

1.6. Cortical reorganization: elderly brain

The results of the studies presented so far suggest that rehabilitative training of cognitive function can restore and even normalize activation. Evidence that neural systems are modifiable networks, and these processes are not limited to the early phases of development were provided, but for the purposes of this dissertation and considering some of the population target of my studies, may be necessary to consider how the aged brain is different when compared to the younger one and whether the older or aged human brain structure changes in response to learning or practicing, just as the younger brain does. Neuroimaging reveals that older brains do things differently, even when performance is comparable to that of younger adults. In their pioneering work Cheryl Grady and colleagues (1992) obtained PET measurements while older and younger adults matched faces or locations. Although older adults were slower, accuracy levels were equivalent and accompanied by pronounced age differences in brain activation: older adults activated dorsal (parietal) and ventral (temporal) sites for both tasks, whereas younger adults showed the expected ventral activation for faces and dorsal

activation for locations. Similarly, Cabeza, Anderson, Locantore and McIntosh (2002) measured prefrontal cortex activity in younger adults, low-performing older adults, and high-performing older adults during recall and source memory of recently studied words. Compared to recall, source memory was associated with right prefrontal cortex activations in younger adults. Low-performing older adults recruited similar right prefrontal cortex regions as young adults, but high-performing older adults engaged prefrontal cortex regions bilaterally. Thus, consistent with the compensation hypothesis and inconsistent with the dedifferentiation hypothesis, a hemispheric asymmetry reduction was found in high-performing but not in low-performing older adults. The results suggest that low-performing older adults recruited a similar network as young adults but used it inefficiently, whereas high-performing older adults counteracted age-related neural decline through a plastic reorganization of neurocognitive networks. Similarly, Reuter-Lorenz et al. (2000) found that the anterior components of the working memory circuitry are bilaterally organized in older adults, whereas younger adults show opposite patterns of laterality for verbal and spatial working memory suggesting that the effects of normal aging on the neural substrate of working memory are selective in the frontal components of the working memory circuitry that show greater vulnerability to aging than the posterior components. The decreased anterior lateralization in older adults may be compensatory, as it reflects the recruitment of additional brain regions to augment task performance. While these studies reported how adult brain and aged brain are differently activated for the same task, very few studies investigated whether training can induce macrostructural changes in older brain. For example, Boyke, Driemeyer, Gaser, Buchel and May (2008) divided a homogeneous group of 93 volunteers (mean age=60) into two groups: training and control. Both groups were inexperienced in terms of juggling at the time point of the first scan. The subjects from the training group were given 3 months to learn classic three-ball cascade juggling. They found that elderly persons were able to learn juggling but with less proficiency compared with 20-year-old adolescents of a previous study (Draganski et al., 2004). Similar to the young group, gray-matter changes in the older brain related to skill acquisition were observed in area hMT/V5 (middle temporal area of the visual cortex). In addition, elderly volunteers who learned to juggle showed transient increases in gray matter in the hippocampus on the left side and in the nucleus accumbens bilaterally. In another study Engvig et al. (2010) examined the short-term effects of an intensive memory training program on cognition and brain structure in middle-aged and elderly healthy volunteers. The memory trainers completed an 8-week training regimen aimed at improving verbal source memory utilizing the Method of Loci (MoL), while control participants did not receive any intervention. Both the memory trainers and the controls underwent magnetic resonance imaging (MRI) scans and memory testing pre and post 8 weeks of training or no training, respectively. The results showed that memory training improved

source memory performance. Memory trainers also showed increases in cortical thickness compared with controls in the right insula, in the left and right lateral orbitofrontal cortex and in the fusiform cortex. Furthermore, thickness change in the right fusiform and lateral orbitofrontal cortex correlated positively with improvement in source memory performance, suggesting a possible functional significance of the structural changes.

1.7. Conclusions

The aim of this chapter was to analyze the most important theoretical base of cognitive rehabilitation: the brain plasticity. I reported the different mechanisms of plasticity both in animal and human studies. Particular relevance for the studies in neuropsychology are all the evidences of plasticity related to learning and directly linked to cognitive training. Showing how mechanisms of cortical reorganization can occur in response to the learning of a task or are directly related to a specific treatment provides the necessary basis for all the cognitive treatment. It means that cognitive rehabilitation holds on a base of neural correlates that are not static and immutable but that can reorganize and plastically mute in response of experience.

Chapter_2 Use of technology for cognition

This second chapter analyses the advancement in technology that are continuously shaping the cognitive rehabilitation. One way in which these effects can be felt is in the growth and development of powerful information-based tools that can be adapted for individuals with cognitive limitations. Increasingly smaller yet more powerful computers and chip-based technology are putting sophisticated devices for storing and retrieving information at our fingertips. Watches, cell phones, paging systems, and hand-held computer devices expand ways in which individuals with physical and/or cognitive impairments can interact with the world. Moreover, as the technological revolution continues to advance, costs and size are coming down, and usability and flexibility are going up. The advancement and development of new assistive technologies can support sophisticated tracking, orienting, and signaling devices for people with severe memory impairments. Individuals with severe physical limitations, even high-spinal-cord injuries, can now interact with their environment through computers signaled by eye movements, or even by keyboards placed on the roof of a person's mouth. Whole apartments have been adapted and wired to support increased independence in the community. Appliances can be monitored for safety; flexible devices for paging or communicating are available; and adapted equipment allows efficient cooking, bathing, cleaning, gardening, and self-care. All of these examples fall under the definition of assistive technologies for cognition (ATC). These can assist people with cognitive impairment (1) providing assurance that the patient is safe and is performing necessary daily activities, and, if not, alerting a caregiver; or (2) helping the patient compensate for his impairment, assisting in the performance of daily activities. These technologies have some advantages: they are easy to use, relatively cheap and do not suffer of social prejudice. However, they have one important limit: they are developed as compensatory strategy for a deficit function. Consequently, the assistive technologies are not designed to improve or to restore the deficit function but just to compensate an impairment without changing the cognitive status of the patients. Even though they are very useful with some specific categories of patients (e.g., the elderly), these technologies will not be the focus of my discussion. Instead, I will focus my discussion on the advancement in technologies used for cognitive training in the context of a cognitive rehabilitation. In particular, I will discuss the literature related to computerized software and to app for cognition that can be found and downloaded for tablet or smartphone devices. Indeed, in the last few years there is a growing attention on all these software that are rapidly replacing the classic tools for rehabilitation such as the paper and pencil exercises.

Before discussing why technology is so important as tool for cognition and the state of the art of his applications it is relevant to underline the differences between cognitive training, cognitive

stimulation and cognitive rehabilitation. The literature is rather confusing since the terms "stimulation", "training" and "rehabilitation" are applied somewhat interchangeably. This tends to obscure some important differences in concept and application. In a review Clare and Woods (2004) aim to offer broad definitions and descriptions of these three approaches and to clarify the underlying concepts and assumptions. Although they focus mostly on early stage Alzheimer disease, the definitions and differences between these approaches can be generalized to other contexts.

The cognitive stimulation involves engagement in a range of group activities and discussions aimed at general enhancement of cognitive and social functioning. Spector, Orrell, Davies, & Woods (2000a, 2000b) conducted two Cochrane Systematic Reviews on the effectiveness of Reality Orientation and Reminiscence therapy as psychological interventions for people with dementia, using evidence from randomized controlled trials (RCTs). From this literature research they developed a program of cognitive stimulation for people with mild to moderate dementia: The Cognitive Stimulation Therapy (CST) (Spector, Orrell, Davies, & Woods, 2001). The therapy is based on implicit learning, stimulating language and executive functioning, with activities focusing on orientation, reminiscence, new ideas, thoughts, and association to promote continuity between treatment sessions. It consists of a four phases program - The Senses, Remembering the past, People and Objects, Everyday practical issues - designed to create an environment in which the subjects have fun, learn, and strengthen their abilities and social relationships among group members and with the operators, maintaining their social and cognitive skills as optimally as possible. Different studies reported the efficacy of this program (Capotosto et al., 2016; Spector et al., 2003; Woods, Aguirre, Spector, & Orrell, 2012). Knapp et al. (2006) reported also a cost-effectiveness analysis highlighting how CST has benefits for cognition and quality of life in dementia, and costs were not different compared to a group of participants that received the usual care. The rationale for the use of a global method of cognitive stimulation, as opposed to a focus on specific functions, rests on the argument that cognitive functions such as memory are not used in isolation. Instead, their operation requires a sophisticated integration with other functions such as attention, language, problem-solving and so on. For this reason, the effectiveness of general cognitive stimulation interventions can only be explored in relation to the whole package, and it is not possible to tease out which particular elements among the various components are the "active ingredients" (Bird, 2000). Perhaps more importantly, it remains to be determined whether the benefits derive mainly, or partly, from the social interaction that is an integral part of the intervention, rather than from the cognition-focused components per se. That is to say, these interventions may be beneficial because they tackle aspects of under-functioning resulting from social environments that are insufficiently stimulating and rewarding, and not because their content focuses on cognition. Although this in itself is a worthwhile goal, it would be useful to

know the precise contribution of the focus on cognition. An evaluation of the specific impact of cognition-focused elements of intervention can more readily be made in relation to cognitive training. In fact, cognitive training involves guided practice on a set of standard tasks designed to reflect particular cognitive functions, such as memory, attention, language or executive function. Cognitive training may be offered through individual sessions (Davis, Massman, & Doody, 2001; Farina et al., 2002; Koltai, Welsh-Bohmer, & Schmechel, 2001; Loewenstein, Acevedo, Czaja, & Duara, 2004), and group sessions (Cahn-Weiner, Malloy, Rebok, & Ott, 2003; Kesslak & Nackoul, 1997; Moore, Sandman, McGrady, & Patrick Kesslak, 2001), or facilitated by caregivers with support of therapist (Neely, Vikstrom, & Josephsson, 2009; Quayhagen et al., 2000). In accordance with the suggestion of Newhouse, Potter, & Levin (1997) that cognitive training may enhance the effects of dementia drug therapy, some studies evaluated the effects of cognitive training in combination with medications (De Vreese, Neri, Fioravanti, Belloi, & Zanetti, 2001; Heiss, Kessler, Mielke, Szelies, & Herholz, 1994; Yesavage, Westphal, & Rush, 1981). Usually a range of difficulty levels is available within a standardized set of tasks, to allow for selection of the level of difficulty that is most appropriate for a given individual. I will discuss later how this will be one of the most important component of the computerized version of cognitive training. The assumptions underlying cognitive training are that regular or routine practice has the potential to improve or at least maintain functioning in a given domain, and that any effects of practice will generalize beyond the immediate training context. Although this latter assumption has not often been supported by some evidence (Owen et al., 2010; Papp, Walsh, & Snyder, 2009), Jaeggi et al. (2010) have argued that the failure to produce transferable benefits is related in part to problems with task design. Outcomes of cognitive training are most commonly assessed through performance on cognitive or neuropsychological tests, with an expectation of improvement or at least maintenance of performance in the treatment group that is not seen in the control group. These approaches appear to be focusing primarily on reducing underlying impairment or arresting its progression, which is a challenging goal. Moreover, some studies do also examine effects on the mood or behavior of the patients, and the impact on the family. Moving the attention forward to more individualized approach and in a way that is consistent with principles of person-centered care we can describe the most recent views of the concept of cognitive rehabilitation. It generally refers to an individualized approach to helping people with cognitive impairments, in which those affected, and their families, work together with health-care professionals to identify personally relevant goals and devise strategies for addressing these (Bahar-Fuchs, Clare, & Woods, 2013; B. a. Wilson, 2002). The emphasis is not on enhancing performance on cognitive tasks but on improving functioning in the everyday context. Cognitive rehabilitation interventions aim to tackle directly those difficulties considered most relevant by the patients and his or her family

members or supporters and target everyday situations in the real-life context. Cognitive rehabilitation approaches tend to be implemented in real-world settings since there is no implicit assumption that changes instituted in one setting would necessarily generalize to another. Goals for intervention are selected collaboratively, and interventions are usually conducted on an individual basis. Based in part on the efficacy and outcome literature, and in part their own experience, Sohlberg and Mateer (2001) have developed a set of principles for implementing effective rehabilitation with individuals who demonstrate cognitive, behavioral, emotional, and psychosocial difficulties following acquired brain injury including: (1) a therapeutic alliance among the therapist, client, and family members or other caregivers; (2) a primary focus on education, with an emphasis on empowerment, self-control, and self-sufficiency; (3) the treatment sessions are structured, and treatment plans and activities are developed with reference to both assessment results and current performance data; (4) is goal-oriented and builds on strengths; (5) it assists clients in achieving a more accurate understanding of their strengths and limitations, and in adjusting to injury-related changes in functioning and in life circumstances.

The reason for the confusion between the terms "training" and "rehabilitation" probably lies in the fact that, in most of the cases, the goals of intervention are also achieved through a training. Often the *cognitive training* represents part of a more general program of *cognitive rehabilitation*. Probably because of this sometimes the terms are used interchangeably.

Anyway, both these approaches are constantly shaped by the development of new technologies: they allow to go beyond several limits of the classic rehabilitation approach. Before the advent of technology such as personal computers or tablets, rehabilitation has relied on paper and pencil tasks provided by a clinician. This method of providing therapy has a great time requirement for clinicians, limiting the number of individuals they can work with at one period of time and is, therefore, also not cost-effective (Jak, Seelye, & Jurick, 2013). Moreover, paper and pencil tasks often are considered boring reducing the patient's motivation (Burdea, 2003). Usually the performance is recorded manually with simple devices (e.g., stopwatch) and thus the accuracy and the amount of data recordable is very low. Therefore, the arrival of technology-based rehabilitation for individuals with acquired brain injury has provided a solution to these issues that face these individuals when they seek rehabilitation. Firstly, one advantage of technology-based tools is interactivity and motivation. This is especially true in video game-based therapeutic approaches where the patient is constantly involved in a challenging task and he feels to compete in order to get the highest score or the highest level of difficulty. By providing visual, auditory and tactile (if possible) feedbacks in real time, patients are motivated to exercise. Relying on computers, the amount and the quality of data stored is definitely more accurate than traditional system. Moreover, these data can be stored in online

encrypted database making data access from remote definitely easy. This represent a great benefit for patients that cannot travel to the clinics: it allows patients to practice the treatment outside of the clinic, increasing opportunities for more rehabilitation than the traditional one-on-one interaction with a clinician and increasing the chance to maintain the progress they made.

There have been many studies and systematic reviews of varied designs and scopes that have examined the effectiveness of technology-based cognitive and language rehabilitation with individuals with acquired brain injury. These have been primarily focused on efficacy of programs at the cognitive impairment level. Some reviews focused on a single cognitive domain: attention (Riccio & French, 2004), executive functions (Bogdanova, Yee, Ho, & Cicerone, 2015), language (Lee & Cherney, 2016; Zheng, Lynch, & Taylor, 2016) .Others addressed multiple cognitive domains within specific neurological conditions: multiple sclerosis (O'Brien, Chiaravalloti, Goverover, & DeLuca, 2008; Rosti-Otajärvi & Hämäläinen, 2014), stroke (Cha & Kim, 2013; Loetscher & Lincoln, 2013; Xu, Ren, Prakash, Vijayadas, & Kumar, 2013), traumatic brain injury (Bayley et al., 2014), and multiple acquired brain injury conditions (Cicerone et al., 2011; Spreij, Visser-Meily, van Heugten, & Nijboer, 2014). In their review Sigmundsdottir, Longley and Tate (2016) evaluated 96 studies that examined the effects of computerized cognitive training across five cognitive domain in patients with acquire brain injury. The first dramatic conclusion they had is that despite the extent of research in this area, the number of controlled trials with good scientific quality was very small, with only 15% of the studies reviewed representing Level 1 evidence (that is, RCTs with PEDro-P scores ≥ 6). Secondly, it was evident that the format of computerized interventions was variable, reflecting the central concepts of remediation vs. compensation approaches in neurorehabilitation. The majority of studies (74%) applied what could be considered a remediation approach, where participants would repeat computerized exercises to strengthen function of one or more cognitive skills, utilizing a variety of commercially available or custom-designed programs. However, there were intervention programs that involved therapist training of participants in the application of compensatory strategies, either specifically related to performance of the computer training (e.g., teaching internal memory strategies that were then rehearsed via computer exercises), or incorporating computer-based training as an element of therapy that also involved other cognitive rehabilitation approaches, such as use of pencil-and-paper exercises, group peer support, psychological support and/or application of compensatory strategies in the participant's daily life.

In terms of evaluating efficacy, the majority of studies used outcome measures at the International Classification of Functioning, Disability and Health (ICF) (WHO, 2001) Body Functions level as their benchmark, with some support evident for improvements on tests of cognitive function following computerized programs for attention (Cerasa et al., 2013; Gehring et al., 2009; Parisi et al.,

2012; Zucchella et al., 2013), working memory (Björkdahl, Akerlund, Svensson, & Esbjörnsson, 2013; Hancock, Bruce, Bruce, & Lynch, 2015; Hildebrandt et al., 2007; Stuifbergen et al., 2012), and speed of information processing (De Giglio et al., 2015) in multiple sclerosis and brain tumor populations. Evaluation of computerized training at the ICF Body Structures level is still an emerging field of research, with only 8% studies included in the review that incorporated neuroimaging outcomes. Most of these studies evaluated neurological mechanisms of change following attention and/or executive training in multiple sclerosis, with some promising findings of fMRI activation increases post-treatment in the right posterior cerebellar lobule and the left superior parietal lobule during performance of a visual attention/working memory task (Cerasa et al., 2013). Also reported have been improvements in functional connectivity measures related to the anterior cingulate cortex and right middle frontal gyrus (Parisi et al., 2012, 2014).

Outcomes reflecting generalization of computerized training to the level of ICF Activities and Participation (A/P) were reported in 43% of the reviewed studies, and the nature measures used were highly variable. These measures included different published scales alongside 14 custom measures, reflecting a spectrum of self, informant and observer ratings of cognition in everyday life, ability during performance of activities, as well as whether or not there is participation in leisure, vocational, social, or educational activities. On these measures there was minimal evidence noted for the impact of computerized training, even at follow-up assessment times of 6–12 months. Most of the controlled group studies reviewed found no changes for participation in activities, such as employment status (Amato et al., 2014; Man, Poon, & Lam, 2013). The only exception was a study presented by Vanderploeg et al. (2008), where it was noted that younger traumatic brain injury participants in the computerized training group had higher rates of return to work than similarly aged controls.

The most commonly utilized measures of A/P were self-report questionnaires assessing frequency of everyday cognitive problems. Nearly all studies found statistically significant improvements; participants reported greater improvements in self-perceived everyday functioning compared with the control participants (Mäntynen et al., 2014).

The number of commercially available computerized training program is rapidly increasing in the last few years. Some of these target one single cognitive domain others multiple domain. Similarly, some software are developed for a specific category of patients, others address different population of patients with cognitive impairments, others are developed as tools for the improvement of cognitive skills for healthy individuals. I will describe some of this software, focusing mostly on the one with a demonstrated efficacy.

One of the most used software is *Cogmed* (Pearson Education, 2000). It is built around three age-specific training programs (pre-schoolers, school-age, adults) for attention problems caused by poor

working memory. The *Cogmed* training method consists of 25 training sessions done online, each 30-45 minutes long. Each session consists of a selection of various tasks that target the different aspects of working memory where the difficulty level is adjusted according to a highly sensitive and specific algorithm. The training is done online at home, in school, or at work. The standard program is five weeks long with five sessions every week. And it is always led by a "*Cogmed* Qualified Coach" who works with the user to provide structure, motivation, and feedback on the progress. During training, the trainee's performance is tracked online and can be viewed by the trainee and his/her *Cogmed* Coach who communicates with the user throughout the five weeks to assist him/her through the program. Several studies examined the effects of *Cogmed* training in different populations. Studies on adolescents or adults with ADHD showed significant improvements in performance-based measures of executive functions, ADHD symptoms, and functional impairment (Bigorra, Garolera, Guijarro, & Hervás, 2015; Mawjee, Woltering, & Tannock, 2015; Roording-Ragetlie, Klip, Buitelaar, & Slaats-Willemse, 2016; Stevens, Gaynor, Bessette, & Pearlson, 2015), albeit Liu, Glizer, Tannock & Woltering (2016) found no training effects on participants' performance concluding that there was no convincing evidence to support changing in the underlying neural networks and a normalization of brain activity due to an intensive working memory training with *Cogmed*. Other evidences supporting the effects of *Cogmed* comes from the studies on brain injured patients (Åkerlund, Esbjörnsson, Sunnerhagen, & Björkdahl, 2013; Björkdahl et al., 2013; Johansson & Tornmalm, 2012; Phillips et al., 2016; Westerberg et al., 2007). For example Hellgren, Samuelsson, Lundqvist & Börsbo (2015) recruited 48 patients with acquired brain injury who participated in a *Cogmed* training. They reported that all patients' working memory index improved after training. Moreover, the cognitive functions, as measured by neuropsychological tests, improved as well as performance of important working memory-related everyday activities and satisfaction with these performances. The subjects estimated a higher quality of life after training compared to before training, and perceived health was improved. There were no gender differences in outcome, but, in contrast with a previous study (Johansson & Tornmalm, 2012) there were significant differences depending on time since injury: the individuals with < 18 months since injury improved more, with respect to working memory index, everyday occupational performance, and satisfaction with that performance, than those with ≥18 months since injury. The *Cogmed* working memory training has been used also in patients with mild cognitive impairment (Vermeij et al., 2016; Vermeij, Claassen, Dautzenberg, & Kessels, 2015), anxiety (Hadwin & Richards, 2016), chronic fatigue (Maroti, Westerberg, Saury, & Bileviciute-Ljungar, 2015), low IQ (Ottersen & Grill, 2015; Söderqvist, Nutley, Ottersen, Grill, & Klingberg, 2012) and post-traumatic stress disorder (Saunders et al., 2015). Another software used for training is the *CogniPlus* (Hauke, Fimm, & Sturm, 2010; Sturm & Willmes, 1991). It consists of fifteen

modules involving interactive game-like tasks. For example, attention tasks involve a first-person view of motorcycle or car driving along a road and require pressing reaction key when obstacles appear (falling trees, braking cars, etc.). Divided attention training involves a simulated task as a security guard monitoring security cameras and loudspeaker announcements. Memory training involves learning face–name associations. Executive modules include training inhibition (in the context of a postal worker finding letters without stamps) as well as planning (identifying an efficient order of tasks to be done using a virtual village map). The program provides graphic feedback of performance to users and has adaptive levels of difficulty (e.g., shorter permitted reaction time, increasing stimulus frequency).

The *NeuropsychOnline.com* is the updated Internet-based version of the *PSSCogRehab* cognitive remediation software described by Chen, Thomas, Glueckauf & Bracy (1997). It consists of five packages aimed at improving performance in four cognitive domains: attention, verbal memory, psychomotor speed and executive function. Initially, participants perform simple tasks in a single cognitive domain (e.g. memory), followed by multi-domain tasks (e.g. memory and attention) and, once successful, graduate to complex tasks that rely upon problem-solving skills. The hallmark of this program is repetition. The program begins with perceptual and attentional tasks, in both the auditory and visual modality. Within each domain, the tasks become increasingly more difficult, requiring, for example, greater periods of sustained attention, or the tracking of multiple cues. The client progresses through each domain, and from one domain to the next, at his or her own pace: each task is repeated until the client has mastered it. The problem-solving tasks at the end of the training regimen build upon and integrate previously trained skills, such as memory, perceptual attention and visual imagination. Some studies examined the effect of *NeuropsychOnline.com* (S. H. Chen et al., 1997; Elgamal, Mckinnon, Ramakrishnan, Joffe, & Macqueen, 2007; Nordvik et al., 2012). For example, Schoenberg et al. (2008), compared outcomes of 19 participants who received the computer-based teletherapy with 20 participants who received face-to-face speech–language rehabilitation. Results showed within group improvement for both cognitive training group and control group on return to work, driving and study. Moreover, there were not group differences: the computer-based teletherapy cognitive rehabilitation program provided similar functional outcomes as face-to-face speech–language therapy at a similar total cost.

The *RehaCom* software (Hasomed GmbH, Magdeburg, Germany) consist of 20 therapy modules. Each module has hundreds of tasks with different levels of difficulty: from very easy to highly complex tasks. The software measures the current performance of the client during course of therapy and automatically switches to the according level of difficulty. Modules are available for a basic therapy of fundamental cognitive functions as well as for therapy of complex daily life abilities.

Fernandez et al. (2012) described the clinical impact of this software on fifty patients with cognitive disorders following stroke or traumatic brain injury. Ninety-seven percent of participants completed all therapy sessions and all cases showed reduced cognitive deficit and reduced completion time for both simple selective attention and executive attention, although the difference was only statistically significant for simple attention. Other evidences supporting the positive effects of using *RehaCom* comes from studies on patients with multiple sclerosis (Mattioli, Stampatori, Zanotti, Parrinello, & Capra, 2010), stroke (Yoo, Yong, Chung, & Yang, 2015), and ADHD (Amonn, Frolich, Breuer, Banaschewski, & Doepfner, 2013).

The *Parrot Software* program (Parrot Software, West Bloomfield, MI) is an interactive Internet rehabilitation platform that is commercially available through Internet access or by CD software. The target populations for the program are individuals presenting with cognitive deficits secondary to stroke and various forms of brain injury. The *Parrot Software* program contains over 100 different modules targeting cognitive reasoning, memory and attention, reading, speech and language, vocabulary and grammar, and word recall. Li, Robertson; Ramos & Gella (2013) evaluated the effectiveness of this software on improving memory and attention deficits in individuals with a chronic acquired brain injury. They recruited twelve adults with a chronic ABI demonstrating deficits in memory and using a quasi-experimental one-group pretest-posttest design, found a significant improvement in both memory and attention scores post-intervention using the cognitive screening tool. In a following study they investigated the generalization effect of a treatment using the *Parrot Software* concluding that it may be a promising intervention for improving global cognition in individuals with acquired brain injury, but additional intervention might be needed for generalization to occur to a novel daily task (Li, Alonso, Chadha, & Pulido, 2015). The same software was used for person with chronic aphasia in an anomia treatment: The Authors found a significant improvement in confrontation naming ability for non- trained words following treatment. Additionally, message informativeness during oral discourse increased for four of the six participants. Moreover, they felt that the treatment employed acceptable procedures and goals, and they expressed overall satisfaction with the intervention program (Corwin, Wells, Koul, & Dembowsky, 2014).

Another software largely investigated and described in literature is *BrainHQ* (Posit Science, San Francisco, CA). It consists of 29 brain-training exercises organized into six categories: Attention, Brain Speed, Memory, People Skills, Intelligence, and Navigation. It takes less than five minutes to do each *BrainHQ* level, so it can be uses in tiny bites or long blocks, depending on patient schedule. Plus, it is available on almost any computer or mobile device. Along the way, the program provides lots of feedback on patient performance - for each level is possible to review the starting score, the improvement and the training effort. The idea is that individuals are not competing against others,

but competing against themselves, working to perform better than they did when they started. Several studies proved that the use of this software brings to improvement in different cognitive functions such as memory (Barnes et al., 2009; Berry et al., 2010; Lebowitz, Dams-O'Connor, & Cantor, 2012; Zelinski et al., 2011), attention (Leung et al., 2015; O'Brien et al., 2013; Van Vleet, Hoang-duc, DeGutis, & Robertson, 2011), mood and locus of control (Morimoto et al., 2014; Wolinsky et al., 2009, 2010), balance and fall risk (Owsley & McGwin, 2004; Smith-Ray et al., 2013; Smith-Ray, Makowski-Woidan, & Hughes, 2014), and processing speed (Ellis, Edwards, Peterson, Roker, & Athilingam, 2014; Rebok et al., 2014; Vance et al., 2007; Wolinsky, Vander Weg, Howren, Jones, & Dotson, 2013). In particular, two important studies proved the efficacy of *BrainHQ*. In the IMPACT study (Smith et al., 2009) 487 adults aged 65 and older were randomized to receive the computerized cognitive training program or an intensity-matched general cognitive stimulation. The duration of training was 1 hour per day, 5 days per week, for 8 weeks, for a total of 40 hours. The primary outcome was a composite score calculated from six subtests of the Repeatable Battery for the Assessment of Neuropsychological Status that use the auditory modality (RBANS Auditory Memory/Attention). Secondary measures were derived from performance on the experimental program, standardized neuropsychological assessments of memory and attention, and participant-reported outcomes. Results have shown a significant greater improvement in the RBANS Auditory Memory/Attention in the experimental group than in the control group. Moreover, multiple secondary measures of memory and attention showed significantly greater improvements in the experimental group (word list total score, word list delayed recall, digits backwards, letter-number sequencing), as did the participant-reported outcome measure. Participants in the experimental group reported significant improvements in their everyday lives. These benefits ranged from remembering a shopping list without having to write it down; to hearing conversations in noisy restaurants more clearly; to being more independent, feeling more self-confident, to finding words more easily and having improved self-esteem in general. In the ACTIVE study (Ball et al., 2002) 2832 persons aged 65 to 94 years recruited from senior housing, community centers, and hospital/clinics in 6 metropolitan areas in the United States were randomly assigned to 1 of 4 groups: 10-session group training for memory (verbal episodic memory; n = 711), or reasoning (ability to solve problems that follow a serial pattern; n = 705), or speed of processing (visual search and identification; n = 712); or a no-contact control group (n = 704). The speed-of-processing training that ACTIVE study participants used was an earlier version of the *BrainHQ* exercise Double Decision (previously called Road Tour). In Double Decision, the user has to spot a target in the middle of the screen while simultaneously noticing a target in the periphery even when they flash on screen very briefly. Each intervention improved the targeted cognitive ability compared with baseline, durable to 2 years.

Eighty-seven percent of speed-, 74% of reasoning-, and 26% of memory-trained participants demonstrated reliable cognitive improvement immediately after the intervention period. These results support the effectiveness and durability of the cognitive training interventions in improving targeted cognitive abilities. Moreover, the only computerized cognitive training exercise used in the ACTIVE study was Double Decision - now found in *BrainHQ* – and it brought to the better cognitive improvement compared to the other training.

Recently, new studies are examining the effects of a new brain training programme: *Lumosity* (Lumos Lab, San Francisco, CA). It consists of 45 games divided into six categories: speed, memory, attention, flexibility, problem solving, and language. The development and validation of *Lumosity* exercises are described in detail in their Authors white paper (Hardy & Scanlon, 2009): "The principles of targeting, adaptivity, novelty, engagement, and completeness are embodied in this suite of games. Each game targets a critical component of brain function. The games are adaptive, increasing challenge as performance improves, and backing off when incorrect responses are made. The games are novel experiences challenging the brain in ways that encourage new connections and improved efficiency. The scientists at Lumos Labs work closely with game developers to create tasks that are both highly effective brain training and highly engaging games. Taken together, the entire suite of games represents a complete brain training system–an entire gym for the brain.". In a first study (Kesler, Lacayo, & Jo, 2011), the software was used with 25 children and adolescents aged 7–19 years with a history of malignancy that involved radiation and/or chemotherapy treatment. The treatment was effective for improving processing speed and cognitive flexibility as well as visual and verbal declarative memory. Improvements in test scores following the intervention occurred even after controlling for age, intervention duration and cancer type. Furthermore, linear modelling demonstrated significantly increased inferior, middle, and superior frontal gyrus activation and decreased reaction time following the intervention compared to baseline. In another study (Zickefoose, Hux, Brown, & Wulf, 2013), the individual growth curve analyses of four participants showed that they made significant improvements in progressing through intervention. However, limited generalization occurred: one participant demonstrated significantly improved performance on one of five probe measures and one other participant showed improved performance on some sub-tests of the Test of Everyday Attention; no other significant generalization results emerged. More recently, Toril, Reales, Mayas & Ballesteros (2016) investigated the effects of a training with *Lumosity* on the visuospatial working memory and episodic memory of healthy older adults. Participants were 19 volunteer older adults, who received 15 1-h training sessions with *Lumosity*, and a control group of 20 healthy older adults. The control group did not receive training but met the experimenter periodically to talk about their activities and other general topics related to aging. The

results showed that the performance of the trainees improved significantly in all the practiced exercises. Most importantly, the Authors found significant enhancements after training in the trained group and no change in the control group in two computerized tasks designed to assess visuospatial working memory: the Corsi blocks task and the Jigsaw puzzle task. Still, some recent studies reported no effects due to this software. Wentink et al. (2016) aimed to determine the effect of a *Lumosity* training program on cognitive functioning, Quality of Life and self-efficacy compared to a control condition in stroke patients. The participants in the control group received weekly information about stroke after log-on at the website of the study. The information provision was not interactive: it provided unidirectional explanations about brain differences between men and woman, the influence of stress on brain function and possible difficulties with living with a damaged brain. The results showed no effect of the training on cognitive functioning, quality of life or self-efficacy when compared to the control condition, except for very limited effects on working memory and speed. Thompson et al. (2016) aimed to assess whether engagement in a memory training program and performing *Lumosity* improves memory function in people with temporal lobe epilepsy. Participants were randomized to one of four conditions: traditional memory training, *Lumosity*, traditional memory training + *Lumosity*, and no training. Results showed that traditional memory rehabilitation techniques can help reduce the burden of memory impairment, but *Lumosity* use was not associated with changes in the memory outcome measures.

Other cognitive program is *CogniFit* available also for mobile devices. The program's training regimen is based on the results of a baseline cognitive evaluation called the "Neuropsychological Examination – CogniFit Personal Coach" (N-CPC). The evaluation is composed of 15 tasks that measure 17 cognitive abilities. Although subjects train on all tasks, the time spent on each task is determined by individual performance. *CogniFit* effects have been examined by several studies focused on working memory and visual memory (Haimov & Shatil, 2013; Peretz et al., 2011; Preiss, Shatil, Cermáková, Cimermanová, & Ram, 2013; Shatil, Metzer, Horvitz, & Miller, 2010), divided attention and planning (Haimov, Hanuka, & Horowitz, 2008; Thompson et al., 2011), processing speed (Verghese, Mahoney, Ambrose, Wang, & Holtzer, 2010) and for enhancing cognitive abilities in elderly people (Gigler, Blomeke, Shatil, Weintraub, & Reber, 2013; Shatil, 2013).

The *SmartBrain Pro* (Educamigos, Barcelona, Spain) is a software with 28 activities designed based on stimulating specific cognitive domains such as attention, working memory, memory, psychomotor speed, executive functions, and visuospatial abilities and nonspecific cognitive exercises such as language, simple calculations skills, and culture. The therapeutic efficacy of *SmartBrain Pro* has been scientifically proven for cognitive impairment due the long-terms treatment of HIV (Becker et al.,

2012), due to Parkinson's disease (París et al., 2011), and due to Alzheimer's disease (Tárraga et al., 2006).

In commerce are available other app for mobile devices or software for computer that are not yet scientifically validated and with ongoing studies examining the effects such as *Neuronation* (Synaptikon GmbH, Berlin, Germany), *Fit Brains* (Rosetta Stone Ltd., Vancouver, Canada), *Memorado* (Memorado GmbH, Berlin, Germany), *Elevate* (Elevate Lab, San Francisco, CA), and *NeuroTablet* (Neurab Srl, Rovereto, Italy).

So far, most of the software described consist of exercise and task for multiple cognitive domains including language. However, there are a lot of computerized and technology-based programs specifically designed for language therapy. Consequently, there have been many studies of varied designs and scopes that have examined the effectiveness of language therapy in either single domain (naming, reading word or sentence and sentence producing) or multiple domains. For instance, one program called *Lingraphica* (The Aphasia Company, Princeton, NJ) is a computer-delivered naming treatment that provides interactive lexical items in a field of semantically related items. One study examined the effectiveness of *Lingraphica* (Aftonomos, Steele, & Wertz, 1997) with no other concurrent therapy and found it elicited gains on all standardized measures (Western Aphasia Battery (WAB, (Kertesz, 1982)), Boston Naming Test (BNT, (Goodglass, Kaplan, & Weintraub, 1983), and Boston Diagnostic Aphasia Examination (BDAE, (Kaplan, 1983)). Another program called *MossTalk* (Moss Rehabilitation Research Institute, Elkins Park, Pennsylvania) is a computer delivered naming treatment that provides various levels of cues to facilitate naming or multimode matching exercises to work on lexical comprehension. Three studies examined the effectiveness of *MossTalk* (Fink, Brecher, Schwartz, & Robey, 2002; Ramsberger & Marie, 2007; Raymer, Kohen, & Saffell, 2006) and found gains in all cohorts for performance within the program and two of the three studies examined and found limited gains on standardized measures (Philadelphia Naming Test (PNT, (Roach, Schwartz, Martin, Grewal, & Brecher, 1996), Philadelphia Repetition Test (PRT, (Dell, Schwartz, Martin, Saffran, & Gagnon, 1997), Philadelphia Oral Reading Test (PORT, part of the PNT), WAB, and BNT). *Multicue* is a program that provides self-cued naming treatment, which has been examined by one study (Doesborgh et al., 2004) that found significant gains on the BNT.

Next, there are several studies that examined computer-based reading treatments. Two studies (Katz & Wertz, 1992, 1997) examined a computer-based hierarchical reading program. One of the studies examined and found improvements on items trained during the treatment program (Katz & Wertz, 1992) and both studies examined and found gains on the PICA and WAB scores. One study (Cherney, 2010) examined a computerized version of *Oral Reading for Language in Aphasia* (ORLA)

treatment, which provided systematic and repeated reading aloud of sentences and paragraphs, which resulted in gains (similar to those treated by clinician) on WAB.

There are several programs that provide sentence processing and/or production treatments through the use of technology. The *AphasiaScripts* program (Rehabilitation Institute of Chicago, Chicago, IL) provides script training treatment with diminishing cues through a virtual therapist to help patients with their speech production skills in a guided context. Three studies examined the effectiveness of *AphasiaScripts* (Cherney & Halper, 2008; Cherney, Kaye, & van Vuuren, 2014; Manheim, Halper, & Cherney, 2009) and found gains for performance within the program and on standardized measures (WAB-R, Communicative Effectiveness Index (CETI, (Lomas et al., 1989), Quality of Communication Life scale (QCL, (Paul-Brown, Frattali, Holland, Thompson, & Caperton, 2003, p.), and the Communication Difficulty subscale of the Burden of Stroke Scale (BOSS, (Doyle et al., 2004)). Another study (Kalinyak-Fliszar et al., 2015) examined a general script training treatment provided through a computer and found that trained scripts generally improved and some patients showed improvement on discourse narratives. Another program called *Sentactics* is a computerized treatment of underlying forms (TUF) treatment provided by a virtual clinician that has been examined in one study (C. K. Thompson, Choy, Holland, & Cole, 2010), which found gains for performance within the program and on standardized measures. Another program called *SentenceShaper* (Psycholinguistic Technologies Inc., Jenkintown, PA) which records patients' spoken words or phrases and allows them to reorder into sentences and narratives. One study examined the effectiveness of *SentenceShaper* (Linebarger, McCall, Virata, & Berndt, 2007) and found gains in the practiced narratives. Lastly, one study (Seron, Deloche, Moulard, & Rousselle, 1980) examined writing treatment delivered with a computer to work on writing to dictation and found improvement on a probe measure.

While all the above studies are examining single domain of language, there are other programs that target multiple language domains, including *iAphasia*, which is a program that provides therapy in six domains (auditory comprehension, reading comprehension, repetition, naming, writing, and reading). One study examined the effectiveness of *iAphasia* (Choi, Park, & Paik, 2016) and found scores improved on the Korean version of the WAB (K-WAB, (Kim & Na, 2004). Another app called *Language Therapy* (Tactus Therapy Solutions Ltd., Vancouver, BC, Canada) provides reading, naming, comprehension, and writing tasks. One study examined the effectiveness of *Language Therapy* (Stark & Warburton, 2016) and found gains on standardized measures. An updated *Lingraphica* program, *TalkPath*, provides a variety of exercises focusing on listening, speaking, reading, and writing. Steele et al. (2014) examined the effectiveness of the program along with remote group and individual therapy sessions and found improvement on several standardized measures.

StepByStep (Steps Consulting Ltd) is a self-managed computer word finding program and exercises involving word-to-picture matching, semantic associate, reading, and spelling. It has been examined in two studies (Mortley, Wade, & Enderby, 2004; Palmer et al., 2012), which found gains in performance within the program.

A few studies have also examined language and cognitive therapy combined. These studies are essentially looking at the interaction between language and cognition and looking at how language tasks can improve cognition and vice versa. One such program is *Constant Therapy* (Constant Therapy Inc., Newton, USA), which provides several domains of language and cognitive tasks including naming, reading, writing, sentence completion, visuo-spatial processing, memory, attention, problem solving, and executive function. Users begin by filling out disorders or conditions for which they have a diagnosis, and the areas they want to improve. Exercises are then specifically customized to each person's needs. The app assesses the user's performance through a variety of visual and audio tasks such as symbol matching, sound identification and auditory command tasks. There are 62 tasks with multiple levels of difficulty. The effectiveness of *Constant Therapy* has been examined in different studies (Kiran, 2016; Kiran, Roches, Balachandran, & Ascenso, 2014; Mark, Onaral, & Ayaz, 2016). Des Roches, Balachandran, Ascenso, Tripodis, & Kiran (2014) recruited 51 individuals with aphasia due to a stroke or traumatic brain injury (TBI) to use *Constant Therapy* for a 10 week therapy program. Participants were split into an experimental group: both experimental and control participants received a 1 h clinic session with a clinician once a week, the experimental participants additionally practiced the therapy at home. Participants did not differ in the duration of the therapy and both groups of participants showed improvement over time in the tasks used for the therapy. However, experimental participants used the application more often and showed greater changes in accuracy and latency on the tasks than the control participants. Furthermore, experimental participants showed more significant and positive changes due to therapy in their standardized tests than control participants.

2.1. What about the Italian context?

In order to complete the analyses on the computer-based solution for cognitive rehabilitation and giving a rationale to this dissertation it is essential to describe the availability of the above-mentioned software in the Italian context. Unfortunately, most of the computerized software cited are not yet provided in Italian language or were not still available when the work described in this dissertation started years ago. In a study (Zucchella et al., 2013) the contents of "Training di riabilitazione cognitiva" (Powell & Malia, 2009) and "Una palestra per la mente" (Gollin, Ferrari, & Peruzzi, 2011) were used as cognitive training for individuals with brain tumor. Fifty-eight patients were randomly assigned to a rehabilitation group or to a control group. The rehabilitation consisted of 16 one-hour

individual sessions of therapist-guided cognitive training, spread over 4 weeks, combining computer exercises and metacognitive training. Patients in the control group received usual care without cognitive training. All patients were evaluated with a comprehensive neuropsychological battery at the admission and after 4 weeks. Patients in the rehabilitation group showed a significant improvement of cognitive functions. In particular, the domains that benefited most from the training were visual attention and verbal memory. The control group exhibited only a slightly, not statistically relevant, enhancement of cognitive performances. For the best of my knowledge this is the only study that proved the efficacy of an Italian computer software. Other software have been developed in Italy but without a scientific proof of efficacy: *ERICA* (Giunti OS, 2014), *COG.I.TO* (Fondazione ASPHI, Bologna) and *NeuroTablet* (Neurab Srl, Rovereto, Italy). The exercises of *ERICA* are divided into 5 categories: attention, memory, spatial cognition, verbal executive functions, non-verbal executive functions. It can be used for cognitive rehabilitation in patients after stroke or traumatic brain injury, for patients with dementia, or for children with learning disabilities. The most important limit of this software is related to the price: the one-year license for the total program and the annual renew have a price completely not affordable for patients that want to practice outside clinic and for the clinician that want to offer this rehabilitation in their clinics. Different the concept of *COG.I.TO*: it is an open-source web application that can be easily downloaded for rehabilitation of attention, memory and language. It provides tables and plots of the performance of patient that are stored in a local database. *Neurab* is a recent startup that developed the *NeuroTablet*, a digital multi-platform system for cognitive rehabilitation. It consists of 40 exercises that can be customized. Exercises are divided into following groups: attention, memory, perception, executive functions, speech, and neglect. Exercises automatically adapt to patient's performance, providing an intense training addressed to all kinds of cognitive levels. Till now research that proving the efficacy of these three software are not known. Rather, some of the software developed in other countries are now available in Italian language. In particular *RehaCom* has been used with Italian population in several studies (Bonavita et al., 2015; Cerasa et al., 2013; Filippi et al., 2012; Mattioli et al., 2010; Mendozzi et al., 1998; Parisi et al., 2012, 2014; Solari et al., 2004). The other software with a proved efficacy in studies conducted outside Italy and only now available also in Italian language are *Brain HQ*, *CogniPlus*, *CogniFit* and *Lumosity*.

2.2. Conclusions

In this chapter the use of new technologies for cognitive rehabilitation has been discussed. The important advantages and the new opportunities offered from computer-based tool for cognitive training and rehabilitation led to the development of different software. Most of them run on computers but in the last few years we are assisting to a rapid increasing of mobile solutions that allows to develop more flexible and easy system for patients of different etiologies. I focused the

discussion mostly on the software that were developed with scientific basis and scientifically proved with studies of efficacy. Furthermore, I examined the availability and the use of these software in Italy: today, some solutions are also available in Italian language, but only two are developed and tested directly in Italy. The lack of these software some years ago led us to the development of the first software for cognitive rehabilitation for mobile devices. In Chapter 4 I will describe the development phase and the features of this software.

Section 1

Chapter_3 Investigating the relationship between standardized tests and therapy exercises: The outcomes of a computer-based treatment for aphasia

Before introducing the software I developed it is important to examine what are the possible ways to describe improvement after a computer-based treatment and if there are relationships between the different dimensions of outcomes. Indeed, all the rehabilitation studies have looked at improvements but in several different ways. One way to look at improvement is to see whether performance into specific exercises delivered by the programs show improvement and to what extent performance on those exercises/sets of stimuli help improve performance on other exercises/sets (i.e., generalization). Another way to examine improvement is to see whether training on the exercises results in improvement on standardized tests. Different studies have examined different measures. It is important to distinguish between impairment-based measures and functional or quality of life (QOL) measures because these reflect two different levels of generalization. Hypothetically, at the first level, treatment is expected to improve performance on the exercise trained, at the next level, this is expected to generalize to untrained times or other exercise. Next, the treatment might influence individuals' scores on impairment-based standardized measures, and followed by scores on functional and QOL measures. This progression illustrates if and how a particular treatment can have wide ranging impact on one's overall quality of life. Another factor worth considering is if the treatment has a long lasting impact on an individual's behavior and this can be assessed in terms of follow-up examinations. So far, these different levels of improvement are reported separately without investigating the possible relationship between the different levels. The aim of this first section is to address this gap in literature looking at the relationship between two different outcomes of a computer-based treatment for aphasia.

Introduction

Each year, around 795.000 in the US experience a new or a recurrent stroke (Mozaffarian et al., 2015). Stroke commonly results in cognitive impairments such as reduced processing speed, neglect, impaired attention and executive dysfunction (Cumming, Marshall, & Lazar, 2013). One of the most prominent focal deficits after stroke is aphasia: the frequency of aphasics among stroke patients ranged from 21% to 38% (Engelter et al., 2006). Consequent language impairments vary in terms of severity and degree of involvement across the modalities of language processing as naming, reading, and writing. Moreover, aphasia has a big impact on emotional well-being that can have a marked negative impact on recovery and response to therapy (Code & Herrmann, 2003). The implications

and the impact of having aphasia for individual themselves and their family highlight the importance of manage the more effective treatment. A recent Cochrane review assesses the effect of speech and language therapy (SLT) and investigates the differences between different SLTs (Brady, Kelly, Godwin, Enderby, & Campbell, 2016). The results showed significant differences between patient whom received SLT and those who did not. Further, social support and stimulation may be beneficial to some aspects of patients' language skills, but the findings were confounded by a significantly higher participant dropout from social support interventions than from SLT interventions (Lincoln, Pickersgill, Hankey, & Hilton, 1982). Moreover, there is insufficient evidence to establish the effectiveness of one SLT theoretical approach over another, with little indication of a difference between group SLT versus one-to- one SLT, and computer-mediated SLT versus therapist-delivered SLT. Lastly, Brady and colleagues observed some benefits to functional communication and severity impairment of high intensity SLT (Godecke, Hird, Lalor, Rai, & Phillips, 2012). Nevertheless, high-intensity approaches to SLT may not suit all participants: significantly more participants in the intensive groups dropped out from these trials than from the non-intensive groups.

Traditional speech-language treatment involves paper-and-pencil tasks provided by a clinician. While this approach is effective there are several limitations. First, this modality is time consuming for clinicians limiting the number of individuals that they can work with in a given period of time. Second, patients frequently have difficulty traveling to a clinic or institute because of their stroke related disabilities. As a result, many patients do not receive the intensity or required frequency of therapy they need to make consistent gains in communication.

In order to remove these barriers, I already discussed the increased interest in aiding rehabilitation through the use of computers and the internet (Choi et al., 2016; Corwin et al., 2014). Technological applications can allow more patient engagement, involvement and control. Further, the use of computer-based treatments allows patients to practice the treatment outside of the clinic, increasing opportunities for more rehabilitation than the traditional one-on-one interaction with a clinician. Recently, two systematic reviews have examined the effects of a technology-based therapy for language deficits. Zheng, Lynch and Taylor (2016) were interested in determining the effect of computer therapy both in comparison to no therapy and in comparison to clinician delivered therapy. They included seven studies, with six studies suitable for determining the effectiveness of computer therapy in comparison to no therapy, and three studies suitable for determining the effectiveness of computer therapy in comparison to clinician- delivered therapy. All six studies investigating computer therapy in comparison to no therapy reported statistically significant improvements within the computer group. Five out of six studies reported statistically significant differences in language outcomes between the computer therapy and control group. All three studies comparing computer-

and clinician- delivered therapy reported improvements in both the clinician and computer-delivered interventions with no statistically significant differences in language outcomes between the two treatment groups. In order to address the specific aims of their systematic review, Zheng only included studies that involved a comparison (e.g., control group, clinician delivered therapy). Consequently, many published computer treatment studies were excluded. Therefore, in their reviews Lee and Cherney (J. B. Lee & Cherney, 2016) used broader criteria to be able to represent a larger range of computer-based treatments. Their purpose was to describe a representative sample of studies from the aphasia literature in which computer-delivery was an integral aspect of the intervention and that could be described as computer-only treatment. Nine out of twelve studies reported positive benefits of computer therapies on cognitive and language measures. As example participants that received a computerized version of treatment of underlying forms (TUF) improved their performance in comprehending and producing both trained and untrained, linguistically related, complex sentences (C. K. Thompson et al., 2010). Participants who received intensive Constant Therapy demonstrated significant gains on standardized measures of language (WAB-R) and cognition (CLQT) as compared to participants who received less intensive treatment (Des Roches et al., 2014). The conclusion we can extrapolate from these reviews is that while rigorous studies, including RCTs and well-designed single case research with replication are still needed to establish the efficacy of specific interventions, computer-based treatments offer many potential benefits to people with aphasia.

The aim of all the studies reviewed is to establish "if", and "how much" a specific computer program or a tablet software could be beneficial for patients. The Authors were interested in understanding if computerized training could improve cognitive functions such as working memory (Åkerlund et al., 2013; Westerberg et al., 2007), attention (Kim, Chun, Kim, & Park, 2011; Zickefoose et al., 2013), or language domains such as naming (Fink et al., 2002), reading (Katz & Wertz, 1997) or writing (Seron, Deloche, Moulard, & Rousselle, 1980). The efficacy of the technology-based therapy could be described as improvement in the specific exercises delivered by the program and on related exercises, or as improvement on standardized tests (ST). Importantly, there have not been attempts to align the exercises provided with computerized training with the ST, as these previous studies were focused on reporting (1) only within task improvement (Crerar, Ellis, & Dean, 1996; Mortley et al., 2004; Ramsberger & Marie, 2007), (2) only improvement on impairment-based ST (Aftonomos et al., 1997; Cherney, 2010; Hoover & Carney, 2014; Linebarger et al., 2007), or (3) both within task improvement and ST improvement separately (Fridriksson et al., 2009; Kalinyak-Fliszar et al., 2015; Kurland, Wilkins, & Stokes, 2014; Raymer et al., 2006). To the best of our knowledge, no study has yet investigated the relationship between these two measures of outcome, and this perceived relationship cannot be automatically assumed. It is important to examine how tasks and ST are

related, if improvement in therapy tasks mirrors improvement in ST. However, there are no studies that prove a predictive relationship that benchmarks gain in treatment with standardized outcome measures. Most of the time the attention is focused on demonstrating the degree of improvement on impairment-based measures from pre-treatment to post-treatment. Moreover, aligning different language and cognitive therapy domains to the ST we are able to define and investigate the specificity of treatment as the specific relationship between individual domains targeted during therapy and the matched ST.

Furthermore, there have been many studies that have examined the effects of treatment dosage on recovery from aphasia comparing the effects of high-intensity treatment compared to low-intensity treatment with different and mixed results (Des Roches et al., 2014; Ramsberger & Marie, 2007; Raymer et al., 2006; Wenke et al., 2014). In this study we were not interested in examining the dosage treatment, rather we wanted to examine if the predictive relationship described above was influenced by the dosage.

The overall goal of the current study was to examine if we could systematically align computer-based impairment treatment exercises with ST measures, addressing the following research goals: (1) are changes in one domain in treatment related to a corresponding ST, thus providing insight into the specificity of treatment? (2) Are these relationships influenced by the dosage of treatment? While establishing the relationship between *changes* in therapy exercises and ST may seem unnecessary and obvious, one of the main issues in aphasia rehabilitation is to validate treatment outcomes on broader outcome measure (Meier, Johnson, Villard, & Kiran, 2016). Further, demonstrating that this relationship is robust enables the future studies examine the effectiveness of computer-based treatment for patients with aphasia.

Methods

Participants

Data used in these analyses come from a previously study (Des Roches et al., 2014). Sixty-four people with language and cognitive deficits were recruited from local hospitals and aphasia centers in the Boston area. The inclusion criteria were broad, only excluding people with dementia. Thirteen individuals dropped out due to medical reasons (n=3), loss of contact or interest (n=4), or due to the study ending before the participants finished the therapy (n=6). There were five participants with a history of traumatic brain injury and the remaining had suffered a stroke. Range in month post onset was from 1 to 359 (M=59.6, SD=69.4). In accordance with the policies set from Boston University Institutional Review Board, informed content was obtained for all participants before their participation in the study. Participants were administered the following standardized language and cognitive tests prior to and at the end of a 10 week therapy program: *Revised - Western Aphasia*

Battery (WAB-R) (Kertesz, 2006) to determine the type and level of aphasia severity; *Boston Naming Test* (BNT) (Goodglass et al., 1983) to determine confrontation naming ability; *Pyramids And Palms Tree* (PAPT) (Howard & Patterson, 1992) to test the participants' semantic access; *Cognitive Linguistic Quick Test* (CLQT) (Helm-Estabrooks, 2001) to determine the relative contribution of cognitive deficits to language dysfunction and to rule out dementia. Two participants did not complete any testing due to inability and unwillingness to complete tests. Refer to **Table 1** for scores and subscores on these tests.

Table 1 *Mean (SD) on standardized test and therapy tasks pre and post therapy. The scores are expressed in %.*

			Pre	Post
Standardized Tests	WAB			
		Naming	61 (34.2)	63.7 (32.5)
		Reading	71.8 (28.1)	69.4 (27.3)
		Writing	60.5 (28.3)	62.8 (28.8)
		CVC*	69.4 (18.8)	70.4 (18.3)
	BNT		47.9 (37.5)	49.5 (36.1)
	PAPT		84.5 (14.8)	86.8 (11.5)
	CLQT			
		Attention	62.6 (30.1)	72.9 (24.1)
		Memory	61.6 (23.4)	63.9 (23.3)
		Ex. Functions	49.1 (20.6)	53.6 (19.5)
		Language	53 (26.9)	55.6 (26)
		Visuospatial	65.7 (25.5)	71.4 (23.3)
Therapy Task domains		Naming	28.3 (16.5)	37 (25.7)
		Reading	34.8 (33.1)	52.2 (34.8)
		Writing	53.8 (24.7)	65.1 (24.2)
		Math	24.6 (30)	42.4 (31.4)
		Visuospatial & Memory	43.6 (30.5)	56.9 (27.4)

* Constructional Visuospatial and Calculation

Therapy Program

The therapy was delivered using the Constant Therapy iOS platform (CT, www.constanttherapy.com). It consists of 34 exercises classified as either language or cognitive tasks (**Figure 1**). The exercises were designed with simple visual configurations and utilized similar methods of response. For each item, instructions were provided both visually and auditory. Auditory instructions and stimuli could be repeated any number of times. For tasks that contained images, the stimuli could be enlarged to the entire screen of the iPad. At the completion of every item, participants were told visually and auditory if their response was correct or incorrect and the correct answer was available for review. Each task was composed of a different number of levels, gradually increasing in task complexity. Each level was practiced until accuracy reached 95% or higher on two or more occasions, at which point the clinician would advance the user either to the next level of difficulty or to a different task if the user was at the highest level. Additionally, if a participant was not improving

on a level or had a performance under 40%, a lower level of that exercise was assigned in addition to or in replacement of the original task, or a different task examining the same skill was assigned. Each participant received an individualized treatment program with the therapy exercises selected based on the strength and weakness in language and cognitive functions identified in the ST. As result of that, not all the patients were trained in all the domains.

All patients received a weekly clinic session. Some of them additionally practiced at home in between the weekly sessions which allowed the measurement of dosage/frequency of therapy. The range of total time of practice goes from 2h and 15min to 110h and 6min (M=32h and 21min, SD=26h and 45min).
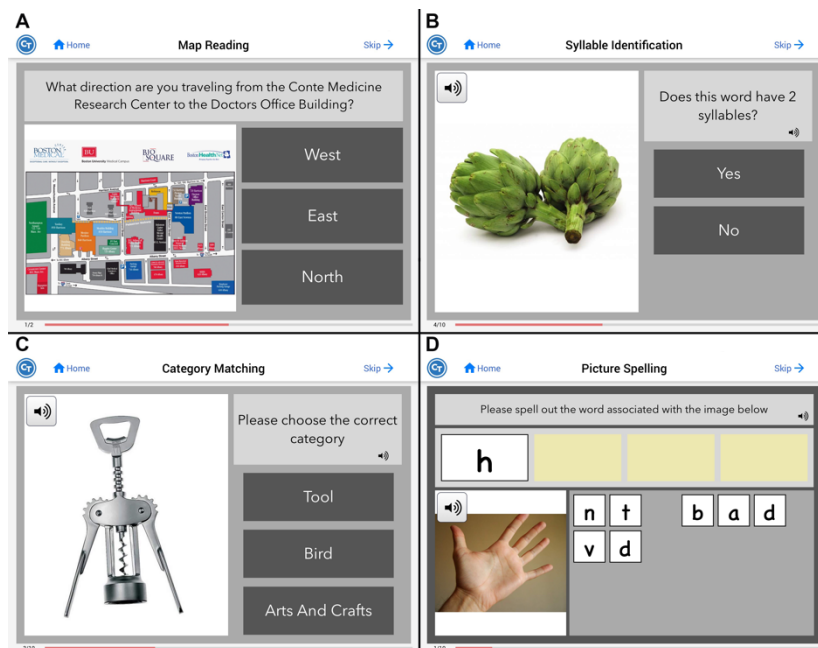
Figure 1 "Constant Therapy" screenshots: A) Map reading; B) Syllable identification; C) Category matching; D) Picture spelling

How to align therapy exercises to Standardized Tests

34 therapy exercises that fit into five domains were targeted in therapy: naming, reading, writing, math, visuospatial & memory. In order to describe how the specificity of CT therapies were aligned to the ST, we proceeded to match all the different tasks with the different ST subtests. Firstly, we looked for an exact match between each of the CT therapy exercise and a specific subtest in the battery of the ST administered. Given that only eleven cases out of 34 therapies had a perfect match with ST, we could not proceed with this approach. Therefore, we had looked at a higher level relationship: between the CT domain and a subscore of the ST. Specifically, each CT exercise was identified for the specific skill that was targeted in treatment and these similar skills were collapsed into a domain (e.g., "addition" and "clock math" were collapsed into the CT Math domain). Likewise, WAB calculation subtests could be collapsed into the WAB construction and visuospatial calculation

domain. In this way, we matched each CT exercise with the related ST subscores, we were able to determine each CT domain to the corresponding ST domains addressing the specific effects we can predict. Refer to **Table 2** for the complete list of matching. It was not possible to find a match for two visuospatial and memory tasks with one specific ST subscore as these therapy tasks were different from what are routinely assessed in ST. As a result of this matching process, we defined the specificity of treatment as relationship between the following domains: CT math and WAB CVC; CT naming and WAB naming, WAB reading, BNT, PAPT and CLQT language; CT reading and WAB reading, WAB naming, CLQT language and CLQT visuospatial; CT writing and WAB writing and WAB reading; CT visuospatial & memory and WAB reading, CLQT memory and CLQT attention.

Table 2 List of all Constant Therapy exercises and their matches with standardized tests

CT-Domain	CT-Exercise	ST-Subtest	ST-Subscore
Math	Addition	WAB Calculation	WAB CVC
Math	Clock Math		WAB CVC
Math	Division	WAB Calculation	WAB CVC
Math	Multiplication	WAB Calculation	WAB CVC
Math	Subtraction	WAB Calculation	WAB CVC
Math	Word Problem		WAB CVC
Naming	Picture Naming	WAB Object Naming, CLQT Confrontation Naming, BNT	WAB Naming, CLQT Language, BNT, PAPT
Naming	Picture Ordering		WAB Naming
Naming	Rhyming		WAB Naming, CLQT Language, BNT, PAPT
Naming	Sound Identification		WAB Naming, CLQT Language, BNT, PAPT
Naming	Syllable Identification		WAB Naming, CLQT Language, BNT, PAPT
Naming	Category Identification		WAB Reading
Reading	Category Matching		WAB Naming
Reading	Feature Matching		WAB Naming, CLQT Language
Reading	Word Identification	WAB Spoken word-written word	WAB Reading
Reading	Word Ordering		WAB Reading
Reading	Instruction Sequencing		WAB Reading
Reading	Long Reading Comprehension		WAB Reading
Reading	Map Reading		CLQT Visuospatial
Reading	Short Reading		WAB Reading
Visuo&Mem	Word Matching		WAB Reading, CLQT Memory
Visuo&Mem	Clock Reading		
Visuo&Mem	Picture Matching		CLQT Memory
Visuo&Mem	Sound Matching		CLQT Memory
Visuo&Mem	Symbol Matching	CLQT Symbol Cancellation	CLQT Attention
Visuo&Mem	Voice Mail		
Writing	Letter to Sound Matching		WAB Reading
Writing	Sound to Letter Matching	WAB Letter Discrimination	WAB Reading
Writing	Word Spelling	WAB Word Spelling	WAB Reading
Writing	Word Spelling Completion	WAB Word Spelling	WAB Reading
Writing	Picture Spelling		WAB Writing
Writing	Picture Spelling Completion		WAB Writing
Writing	Word Copy	WAB Copying a sentence	WAB Writing
Writing	Word Copy Completion		WAB Writing

Visuo&Mem, Visuospatial & Memory; CVC, Constructional Visuospatial and Calculation

Calculating the dependent measures

The Constant Therapy software provides detailed reports for each performance of the patient. In particular, it provides averaged accuracy and latency for every session specific to each exercise the participant completed. However, to be able to compare data across participants across the 34 different therapy exercises across domains, it was important to normalize the different levels of performance for each exercise. But how should different difficulties of each exercise within a domain be compared? If we limit our view on rough accuracies, we can't distinguish between an 80% accuracy

on an easy exercise and 80% in a harder one, or to distinguish between an 90% accuracy in level 1 of an exercises and 90% accuracy in level 4 of the same exercise. To solve this issue, we weighted the accuracy of each exercises & level by its occurrence order within the Constant Therapy progression for that domain: Indeed, tables of progression order of the exercises were created for each domain using a carefully thought-out curriculum to gradually progress the user from easy basic tasks up through increasingly more complex tasks while maintaining a constant level of challenge for the user. This progression order is a way to estimate difficulty when comparing a single exercises & level to all other levels and exercises within a domain. Refer to **Table 3** for an example of the progression order of Constant Therapy's math domain.

Table 3 Table with the progression order used for Constant Therapy's Math domain

Task Name	Task Level	Progression Order
Addition	1	0
Addition	2	1
Addition	3	2
Addition	4	3
Addition	5	4
Subtraction	1	5
Subtraction	2	6
Subtraction	3	7
Subtraction	4	8
Subtraction	5	9
Multiplication	1	10
Multiplication	2	11
Multiplication	3	12
Multiplication	4	13
Multiplication	5	14
Division	1	15
Division	2	16
Division	3	17
Division	4	18
Division	5	19
Word Problem	1	20
Word Problem	2	21
Word Problem	3	22
Word Problem	4	23
Word Problem	5	24
Clock Math	1	25
Clock Math	2	26
Clock Math	3	27

Then instead of raw accuracies, using the progression order value, a normalized score (NS) was calculated with the following formula:

$$NS = \frac{Progression\ Order\ Value\ +\ (accuracy\ -\ .40)}{(.95\ -\ .40) * N.\ of\ total\ levels\ in\ domain}$$

This formula takes into consideration the upper and lower accuracy limits used during therapy to move from an exercises to another in order to equalize the transition point from one exercise to another. With this formula, a domain score at 95% accuracy in task 1 (the cut-off for task advancement) will equal 40% in task 2 (the cut-off for task regression) The scores were also weighted for the number of total levels in a specific domain so that the range of the NS for each domain would fall roughly between 0 and 1.

To run the statistical analyses on improvement in therapy, however, the NS data needed to be collapsed in a way that allowed comparison of a baseline score with a post-therapy score for each domain. We did not want to blindly use the first and last data points in the timeline because they can produce some distortion of the real status of patient. For example, if we consider the very first time a patient did a math exercises and obtained an accuracy of 100% in addition level 1, this does not mean their current ability level is at addition level 1, only that their ability level lays above that exercise. Hence, after clipping the first data point, we considered performance that was associated with less than 95% accuracy in the next three sessions as the baseline score. This score would indicate the real level of a patient because this is the point at which they begin to display difficulty completing the exercises.

The same criterion was applied to get the correct end point. We didn't use the last time point because he doesn't necessarily indicate the true level of a participant: for some reason he could have had an easy exercise at the very end with a high accuracy or at the opposite he could have had a temporary bad performance. For this reason, we considered the last few sessions looking backward to the first normalized score associated to an accuracy below 95%.

Data Analysis

We used the pre-treatment and post-treatment NS values in linear models as predictors for the post-treatment ST scores. The results do not need to be adjusted for multiple comparison because each model is assessing the interaction between one ST and one CT domain. We also ran Monte Carlo simulations to examine if our results were due to chance, and a K-fold cross validation analysis to estimate how accurately our predictive models will perform with different subset of data.

All the analyses were completed using the software RStudio (Rs. Team, 2015) with R version 3.3.0 (R. C. Team, 2016) and the packages *cvTools* (Alfons, 2012)*, DAAG* (Maindonald & Braun, 2014)*, effects* (Fox, 2003)*, ggplot2* (Wickham, 2009)*,*and *stargazer* (Hlavac, 2015).

Results

To first demonstrate that we had accurately aligned the CT therapy tasks with the ST, we performed correlations (**Table 4** Correlation Coefficient between CT pre-scores and the aligned ST pre-scores.**Table 4**) that confirmed that the CT therapy tasks were indeed captured in the ST tasks selected. In order to answer to our question, we could use two linear models (M1 and M2), which differ in the predictors they consider. While M1 used only the post-treatment CT score to predict the post-treatment ST score, M2 used the post-treatment CT scores controlled for the pre-treatment scores, therefore accounting for individual performance at the beginning of treatment. Compared to M1, M2 allows the consideration of the potentially high variability and the unique profile of each individual. Moreover, each patient had a different and personalized program and, therefore, each individuals'

responsiveness to treatment could be different. For these reasons, even though M1 and M2 were performed, we only discuss the results of the M2 as it is a more accurate representation of the data.

Table 4 *Correlation Coefficient between CT pre-scores and the aligned ST pre-scores.*
*p<0.05; **p<0.01; ***p<0.001

CT-Domain	ST-Subscore	*Correlation*
Naming	WAB Naming	0.541***
	WAB Reading	0.444***
	BNT	0.541***
	PAPT	0.291*
	CLQT Language	0.594***
Reading	WAB Naming	0.658***
	WAB Reading	0.649***
	CLQT Language	0.679***
	CLQT Visuospatial	0.388**
Writing	WAB Reading	0.631***
	WAB Writing	0.562***
Math	WAB CVC	0.506***
Visuo&Mem	WAB Reading	0.461***
	CLQT Memory	0.457***
	CLQT Attention	0.109

CVC, Constructiona Visuospatial & Calculation;
Visuo&Mem, Visuospatial and Memory

The results show that the model considered (M2) is statistically significant with a significant effect of the Post CT score in the prediction of the ST score (**Table 5**). As result of the matching process, we were specifically interested in looking at the relationships highlighted by the process described above: the models with CT naming scores as predictors are significant for WAB naming ($F_{(2,42)}$=13.682, p<.001), WAB reading ($F_{(2,42)}$=8.541, p<.001), BNT ($F_{(2,42)}$=15.613, p<.001), PAPT ($F_{(2,40)}$=4.304, p=.02) and CLQT language ($F_{(2,41)}$=11.995, p<.001); the models with CT reading scores as predictors are significant for WAB reading ($F_{(2,45)}$=56.848, p<.001), WAB naming ($F_{(2,45)}$=36.126, p<.001), CLQT language ($F_{(2,44)}$=28.376, p<.001) and CLQT visuospatial ($F_{(2,44)}$=8.047, p=.001); the models with CT writing scores as predictors are significant for WAB writing ($F_{(2,37)}$=10.057, p<.001) and WAB reading ($F_{(2,39)}$=17.149, p<.001); the model with CT math scores as predictors is significant for WAB constructional, visuospatial and calculation ($F_{(2,28)}$=17.092, p<.001); the models with CT visuospatial as predictors are significant for WAB reading ($F_{(2,42)}$=5.549, p=.007) and CLQT memory ($F_{(2,41)}$=6.294, p=.004). Although in these last two cases the overall models are significant there were no effect of CT visuospatial post-scores. Also, we did not find an effect on CT writing post-scores on ST reading. Furthermore, we did find effects of CT post-scores on other ST in addition to our intended comparisons: for instance, CT naming scores had significant effects on WAB writing and CLQT memory.

Table 5 *Regression coefficient of CT post-scores with R squared of the model in parenthesis. Each cell shows the results of a model with the corresponding CT domain as predictors of the ST. In bold the models where we predict a significant effect thanks to the matching process.*

	WAB Naming	WAB Reading	WAB Writing	WAB CVC	BNT	PAPT
CT naming Post	**0.549**** **(0.394)**	**0.485**** **(0.289)**	0.493** (0.254)	0.237 (0.241)	**0.639**** **(0.426)**	**0.193*** **(0.177)**
CT reading Post	**0.567***** **(0.616)**	**0.650***** **(0.716)**	0.528*** (0.520)	0.222* (0.364)	0.544*** (0.622)	0.155* (0.359)
CT writing Post	0.597* (0.423)	**0.370 (0.441)**	**0.454*** **(0.352)**	0.375* (0.347)	0.625* (0.487)	0.175 (0.228)
CT math Post	0.278 (0.189)	0.255 (0.178)	0.331 (0.215)	**0.312***** **(0.550)**	0.563* (0.282)	0.156* (0.261)
CT Visuo&Mem Post	0.045 (0.200)	**0.171 (0.209)**	0.068 (0.098)	0.112 (0.168)	0.173 (0.200)	-0.004 (0.143)
	CLQT Language	CLQT Visuospatial	CLQT Memory	CLQT Attention	CLQT Executive Functions	
CT naming Post	**0.345*** **(0.338)**	0.267 (0.133)	0.323* (0.353)	0.242 (0.119)	0.179 (0.179)	
CT reading Post	**0.391***** **(0.543)**	**0.295* (0.235)**	0.347** (0.517)	0.317* (0.272)	0.196 (0.312)	
CT writing Post	0.388 (0.414)	0.355 (0.172)	0.319 (0.452)	0.396 (0.165)	0.309 (0.225)	
CT math Post	0.240 (0.236)	0.238 (0.271)	0.252 (0.271)	0.219 (0.133)	0.214* (0.415)	
CT Visuo&Mem Post	0.083 (0.235)	0.080 (0.039)	**0.094** **(0.235)**	**0.057** **(0.048)**	0.119 (0.089)	

$*p<0.05; **p<0.01; ***p<0.001$

In order to test if these results were due to chance the F statistics were validated using Monte Carlo simulations. In each simulation (10,000 for each model) all the values of the variables of the model were shuffled with replacement and an F statistic of the model with these variables simulated was calculated. The final distribution of the 10,000 F calculated allowed us to determine the percentile of the original F. In every case, the F of the model with the observed variables was over the 95% of the distribution of the simulated F. See **Figure 2** for an example of F simulated for WAB naming
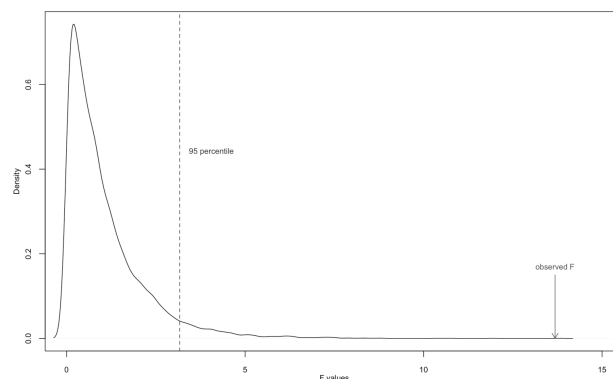
Figure 2 Distribution of 10.000 simulated F with marked 95 percentile of distribution and the original observed F

Moreover, all these models were validated using a cross validation analyses. We used a K-fold cross-validation for assessing how the results will generalize to an independent data-set: we wanted to estimate how accurately our predictive model will perform with different sub set. In the k-fold cross-

validation, the original sample of data is randomly partitioned into k folds of roughly equal size. Of the k subsamples, a single subsample is retained as the validation data for testing the model, and the remaining $k - 1$ subsamples are used as training data. The same operation is repeated for each fold and the model's performance is calculated by averaging the errors across the different test sets. We used 5 folds for our analyses. The cross validation residuals sum of squares were low and ranged from 0.009 (WAB constructional, visuospatial and calculation) to 0.09 (BNT) indicating a very good prediction ability. Refer to **Figure 3** for an example plot of each fold's predicted values against the actual outcome observed in reading domain as a representative sample.
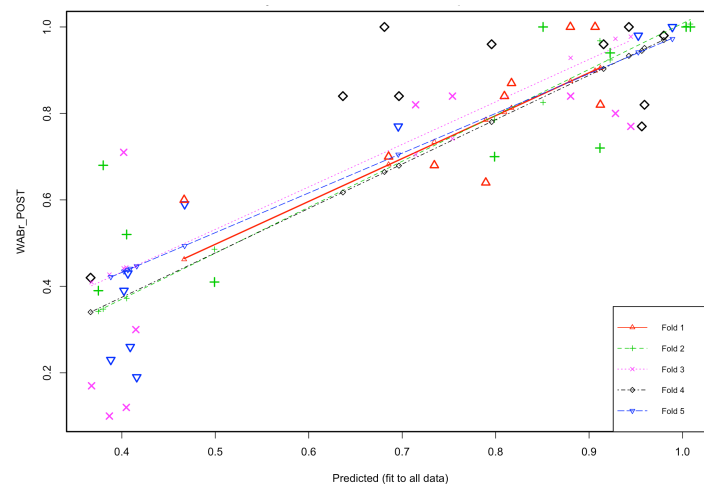
Figure 3 *Predicted values against actual values for each fold for Reading Domain. Each fold has a different symbol with a different regression line. The small symbols in the regression lines are the predicted values, the big symbols in the same vertical axis are the observed value.*

Lastly, we repeated all the models by adding the hours of therapy as a new explanatory variable to see if there was a significant effect of the intensity of treatment on the relationship between therapy outcome and standardized test performance. None of the models showed a significant effect of the hours of treatment.

Discussion

In recent years, the use of technology to address new opportunities for rehabilitation of cognitive functions in patient with acquired brain injury has been discussed in different reviews (Bogdanova et al., 2015; Lee & Cherney, 2016; Sigmundsdottir et al., 2016; Zheng et al., 2016). The clinical effectiveness of technology-based therapies is examined in different studies reviewed both for cognitive deficits (Couillet et al., 2010; Richter, Mödden, Eling, & Hildebrandt, 2015) and language deficits (Des Roches et al., 2014; Fink et al., 2002). These studies were focused on the potential benefits derived from the technology-based treatment. In contrast, the goal of this study was to examine the relationship between how post-treatment performance on therapy exercises was related to post-treatment gains on the standardized tests using a technology-based therapy. While previous studies were focused on reporting (1) only within exercise improvement (Crerar et al., 1996; Mortley

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et al., 2004; Ramsberger & Marie, 2007), (2) only improvement on impairment-based standardized measures (Aftonomos et al., 1997; Cherney, 2010; Hoover & Carney, 2014; Linebarger et al., 2007), or (3) both within exercise improvement and standardized tests improvement separately (Fridriksson et al., 2009; Kalinyak-Fliszar et al., 2015; Kurland et al., 2014; Raymer et al., 2006), we investigated how these two different measures of outcome were related. First, we attempted to align each CT task to different ST subscore. We described a process that was applied to the therapy tasks and the ST utilized in this study, but this approach can be extended to align any computerized exercises to any corresponding outcome measure. This is an important novel contribution of this study. The result of this process sets up possible relationships between treatment tasks and ST and in this study, we are able to define the specificity of a treatment task/domain on corresponding STs (**Table 2**). Establishing such a relationship strengthens the validity and efficacy of the various impairment-related treatment that are utilized in aphasia rehabilitation. To the best of our knowledge, no study has investigated such a relationship before.

Results show a significant effect of CT post-treatment normalized score, controlled for the CT pre-treatment score, in the prediction of the ST in all the expected cases (the bold results on **Table 5**). Surprisingly, we did not find an effect of CT writing post-score as predictor of WAB reading: in this case the pre-scores account for most of the variability. Notably, the strongest predictive relationships were observed for naming and reading. Further, we found that CT Visuospatial and memory scores were not significant predictors for any of the ST. It is possible that the tasks within this domain require skill that are not adequately revealed by the ST: for instance, picture matching, sound matching and symbol matching may tap into short-term memory differently than what STs capture.

Furthermore, we found other effects that we did not predicted. These results are justifiable by the specific feature of Constant Therapy exercises that concurrently target more than one domains. Most of the exercises require simultaneously reading abilities and semantic access. This can explain the effects of CT reading, naming and writing scores on most of the ST and also the effect of CT math on BNT and PAPT. Notably, the Monte Carlo simulations ascertained that these relationships were not due to chance.

Lastly, we were interested in investigating if all these relationships were influenced by the dosage of a treatment. any relationship between treatment and ST outcome should be an intrinsic property of the treatment and the ST used, and consequently, should not differ between individuals in response to their therapy dosage. The results confirm this hypothesis.

These results illustrate a method to align the treatment tasks with the ST. This is true for the specific of the software used for the rehabilitation, the "Constant Therapy", and the STs selected to measure improvements overtime. However, we described a method that can easily generalized to other

treatment contexts and with different software and ST. This entire process should be considered when describing improvements on standardized measure of outcome as result of a therapy program because it can help to confirm the hypothesis about possible effects of treatment. Finally, it has important implications for studying the effectiveness of computer-based treatments.

Conclusions

The main goal of this study was to examine the possibility of benchmark change overtime of performance in therapy exercises with the outcome of the treatment as measured by the standardized tests. Usually these two dimensions of outcomes are reported and considered separately, and the presence of a relationship between these is taken for granted and never investigated. While establishing the relationship between changes in therapy exercises and ST may seem unnecessary as it seem so obvious, it has an important implication: establishing such a relationship strengthens the validity and efficacy of the various impairment-related treatment that are utilized in cognitive rehabilitation. Finding a predictive relation between therapy exercises' performance overtime and standardized score could confirm that outcomes of treatment are directly connected to the treatment each patient received and specifically to the unique response of each patient to that. It would confirm that changes in performance on therapy exercises and in standardized tests are not just in co-occurrence but are directly related each other and this relation allows the clinician to make predictions. Results demonstrate that this predictive relationship exists: in all the expected cases there is a significant effect of post-treatment normalized score on computer-based exercises, controlled for the pre-treatment score, in the prediction of the standardized tests. These results were strongly confirmed by further analyses, such as the Monte Carlo simulations and the K-fold cross validation, directed to exclude chance effects and to assess predictive power of the model used. The second important implication of these study is the description of a method useful to align the computerized exercises administered during treatment and the standardized measure used for assess the effects of a treatment. Although in this study it is specifically related to the computerized app and the standardized tests used, we described a process that can easily extended to other contexts. The most important steps of this process are: (1) the definition of a progression order of the exercise in order to allow a normalization of the accuracies between exercises and within different levels of the same exercise; (2) the definition of an accurate baseline and end-point of treatment, in order to avoid distortions of the real status of the patients; (3) a solid and accurate alignment between the cognitive functions involved in the computer-based exercises and the similar skill assessed by the standardized tests in order to predict the specific effects of treatment.

Section 2

Chapter_4 The Padua Rehabilitation Tool

In Chapter 2 I described the wide range of computer-based software for cognitive rehabilitation. Unfortunately, until few years ago most of them were unavailable for Italian population. Furthermore, the overview of software for touch-screen devices consisted only of game for brain but none of these was specifically developed for patients and therefore they have some limits when used from population with cognitive impairments. Indeed, from a programmer's viewpoint, the advice given for the production of therapy software is rather general. The standards suggested by Newell (1985) and Lynch (1988) highlighted what was accepted as best practice. For example, these includes: (1) simplicity, not making the users do unnecessary works, (2) flexibility, allowing user to specify such parameters as levels of difficulty, exposure times or time limits, (3) a decent documentation containing information concerning what the software is, as well how to use it, and (4) continuous support. While it is true that few programs are written at the highest standards, therapists could perhaps contribute more by emphasizing where a programmer should be expected to go beyond normal standards to suit the demands of particular user group such as patient with cognitive impairments. Possible suggestions could perhaps be for more extensive user testing than would be expected for a normal software; for paying more attention to the human computer interface of the program taking account of patients with, for example, visual impairments, attentional problems and speech problems; and consideration of the patient input/accessing problems, such as through motor problems in using a keyboard or visuospatial problems when using a mouse, joystick or trackball. While saying that a software must be written by a professional programmer because a clinician is unlikely to have the necessary skills or time, it is equally true that a programmer is unlikely to have the requisite knowledge of therapy to write suitable software. In order to develop a software with the necessary quality and efficacy is required a collaboration of professional in both fields. McBain and Renton (1997) stated that "ideally, a programmer who has the knowledge and experience to exploit the capabilities of the hardware used and implement an effective program should work with a therapist who would guide the theoretical and clinical application aspects of the software." This statement today is still valid but the advancement in technology and in language programming allow nonprofessional programmers to develop app and software. It means that is still true that a programmer needs a therapist to develop a valid and efficient software for population with cognitive impairments, but it is not true anymore that a therapist needs a programmer to develop the same software. Surely, the development phase require much more time for a therapist than a programmer but on the other hand is reduced the time needed to make all the adjustments avoiding the frequent back and forth of the software from the therapist to the programmer and vice versa. Particularly in

the early stage of development the figure of therapist and programmer can be overlapped. Years ago, this awareness together with the lack of valid tools in Italy led us to the decision of developing by ourselves the first software for cognitive rehabilitation in Italian language using the touch-screen technology. In particular, we started deciding to convert a previous tool developed for Nintendo Wii to the touch-screen technology. In fact in previous studies (Cardullo, Seraglia, Bordin, & Gamberini, 2011; Gamberini, Cardullo, Seraglia, & Bordin, 2010) we developed and tested the efficacy of 4 exercises for cognitive training in elderly people. Our results showed significant improvement in measure of general cognitive functioning and in some memory tests in individuals that used the computer-based exercises twice a week for three months compared to the control group. However, despite the positive and promising results we observed some limits of the Nintendo Wii technology, in particularly related to the controller. Indeed, albeit the Nintendo Wii remote provides a new interface rationale that involves natural physical interactions we observed some difficulties in patients in understanding how the movement of the cursor on the virtual environment are directly related to the speed and the width of the physical movement of the arm. The tablet devices were released more or less the same year (end of 2010-2011) and then we decided to go beyond this usability problem converting our software for tablet taking advantage of the touch-screen technology: this is the input to the origin of the "Padua Rehabilitation Tool" (PRT). Below are discussed the features of this software and described the exercises included.

4.1.   Software architecture

The PRT has been programmed with the different versions of Adobe® Flash® Professional (CS5, CS6, & CC) using ActionScript 3.0 as programming language. Adobe Flash is a multimedia software platform for production of animations, browser games, rich Internet applications, desktop applications, mobile applications and mobile games. Flash displays text, vector graphics and raster graphics to provide animations, video games and applications. It allows streaming of audio and video, and can capture mouse, keyboard, microphone and camera input. End-users can view Flash content using Flash Player (for web-browser) or Adobe AIR (for desktop or mobile applications). Historically Flash was largely used in the early 2000s. It was widely installed on desktop computers, and commonly used to display interactive web pages, online games, and to playback video and audio content. For example, YouTube used Flash Player as a means to display compressed video content on the web. However, after the 2000s, the usage of Flash on Web sites declined and today it is used primarily to build video games for mobile devices with Adobe AIR. ActionScript 3.0 is a powerful, object-oriented programming language based on ECMAScript, the international standardized programming language for scripting. In object-oriented programming language programmers define not only the data type of a data structure, but also the types of operations (functions) that can be

applied to the data structure. Basically, the programmer can create some "objects" and apply some functions to this objects (e.g., a green circle with the function of a button). All the objects and the functions are organized in a Timeline composed by the single frames of the specific exercises (e.g., the first frame with the instruction, the frame with positive feedback…). For moving from a frame to another are used different functions related to the action of user (e.g., if tap on a figure go to the next frame). Each exercise has a different timeline but they are all listed in the same file. See **Figure 4**, for a screenshot of the program with an example of code.
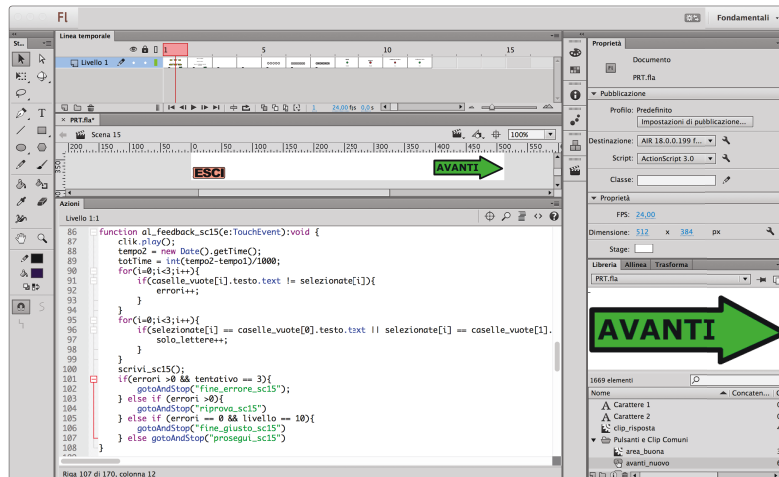
Figure 4 *Screenshot of Adobe® Flash® Professional CC*

Adobe® Flash® Professional allows to publish the app for both Android and iOS systems and today the application has been tested and used with all versions of iPad. I have written all the code and developed the entire application.

All the audio contents and most of the images utilized in the various exercises are marked with Creative Commons 0 (CC0). The person who associated a work with this deed has dedicated the work to the public domain by waiving all of his or her rights to the work worldwide under copyright law, including all related and neighboring rights, to the extent allowed by law. It is possible to copy, modify, distribute and perform the work, even for commercial purposes, all without asking permission. The rest of the images were created ad hoc or were digitalized from "Demenza. 100 esercizi di stimolazione cognitiva" (Bergamaschi, Iannizzi, Mondini, & Mapelli, 2008) with the permission of the Authors.

All the data with the users' performance are stored in a SQLite database saves in the local devices. It is encrypted and can be downloaded connecting the device to a computer. Anyway, the app it is not in commerce and then it is personally installed on a limited number of devices of the collaborators that used and tested the app.

4.2. Tablet and Touch-screen technology

I already mentioned the importance and the reasons that led us to the development of a software that use the touch-screen technology. The capacitive touch-screen technology has been described for the first time by Johnson in a short article in 1965 and then more fully with diagrams and photographs in 1967. We have to wait 1983 to see the first commercialized computers with touch-screen: the HP-150. It is with the release in 1996 by the Palm, Inc, of the first of the Palm OS based PalmPilot touch and stylus based personal data assistant (PDA) that the touch-screen technology met the world of the mobile devices. During the 2000s we assist to the development of the first generation of tablet computer and PDA. These mobile computing devices have been adopted increasingly in all healthcare settings to support the information and communication needs of clinicians. However, most of the empirical research on mobile computing in healthcare has focused on mobile phones, PDAs, traditional laptops, and convertible laptops (with a screen that can be flipped to create a tablet-style PC) (Cockerham, 2009; Horsley & Forster, 2005; Yi, Jackson, Park, & Probst, 2006). What these studies have found is that PDAs and mobile phones, while extremely portable, have been limited in their usefulness by their small screen size and inadequate software. In a review of the literature on PDA adoption, Lu, Xiao, Sears & Jacko (2005) found that one of the major barriers to adoption was usability. Laptops, on the other hand, provide a more traditional computing experience with access to more software options, but are generally too bulky and heavy for true portability.

But it is in 2010 that we assist to the beginning of a new era of tablet devices and their incredible diffusion among population. As a matter of fact, in 2010, Apple, Inc. introduced the iPad as the first in a growing category of tablet devices designed to fill the gap between phones/PDAs and laptops. Pitt, Berthon and Robson (2011) highlight the features of the Apple iPad that make contemporary tablet computers more appealing for use in the workplace, including: an almost ideal screen size, very portable, always/instant on, very long battery life, ease of use, accelerometer and gyroscope, and global positioning system (GPS).

Obviously the main reason that make the tablet device also a valid tool for developing computer-based software for cognitive rehabilitation rely on the touch-screen component. Since touch-screens literally put the fingers in touch with what is on the tablet screen, this technology is considered as the most natural of all input devices. The most obvious advantage is that the input device is also the output device. Being able to touch, feel and manipulate objects on the screen, in addition to seeing and hearing them, provides a sense of immersion. Surely, this is a big step forward in the usability of a system particularly if compared to classic input devices such as keyboard or mouse or recent input such as the Nintendo Wii Remote that require much more hand-eye coordination. For most of the gesture users do not need a training to learn how to interact with the touch-screen because it is

extremely intuitive. For this reason, the only gestures that are required to complete the exercises included in the PRT are the "tap", "pan" and in only one cases the "rotate" (see **Figure 5**). Furthermore, is much more easy for patient with motor problem on the dominant hand to interact with the screen with the non-dominant hand: learn how to use a mouse with the non-dominant hand requires much more time and efforts. Moreover, the touch-screen technology is sensible not only to the fingertips but to other part of the body as example the knuckles or the palm of the hand.
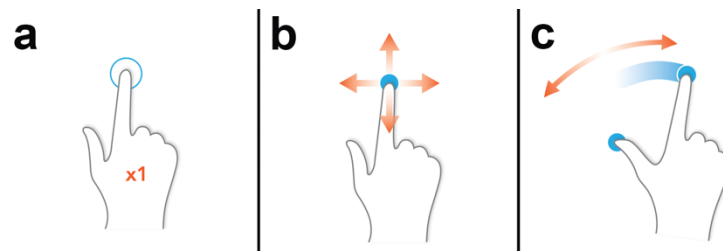
Figure 5 Gesture required into the "Padua Rehabilitation Tool": (a) Tap; (b) Pan; (c) Rotate

Other important advantage in using a tablet computer for delivering rehabilitation is that it is a mobile device and it can be easily moved wherever the patient and the therapist needs. It allows as example to deliver the rehabilitation directly to the bed in case of patient in intensive therapy. In this way it is possible to provide an intervention in the very early stage after a trauma.

Lastly, the diffusion of tablet computers among population is rapidly increased in the last five years. In a report relative to the U.S population the tablet-computer ownership has increased from 3% to 45% since 2010 (Anderson, 2015). Thanks to the low costs this technology is widely diffused among population and as consequence of that, valid cognitive software for rehabilitation can easily be used by a large amount of population without additional costs.

4.3.   Theoretical Background

One of the strong points of the PRT is that the exercises developed rely on solid and scientific theoretical basis. When we started to build the software this was an important difference compared to the existent tools. The first computer-based software were prevalently developed for healthy people and commercialized as games for exercise the brain of patients with cognitive impairment (e.g. *Big Brain Academy*, Nintendo). Moreover, the attention of scientists was focused on investigate the effects of video games on cognitive abilities (Kueider, Parisi, Gross, & Rebok, 2012). The first study that hypothesized positive effects of an arcade video games (*Crystal Castles*, Atari) on perceptual motor skills and cognitive functioning of older adults, dates back to 1986 (Drew & Waters, 1986). After an 8-week training, participants significantly improved on global measures of cognition (WAIS-R) and psychomotor speed, whereas controls showed no improvements. One year later Clark and colleagues (1987) studied the effect of playing *Pac-Man* or *Donkey-Kong* on processing speed for seven weeks. Results indicated at post-test, the mean reaction time for the intervention group was

faster compared with controls on both compatible (responded to stimuli directly in front of their finger) and incompatible (responded to stimuli opposite of their finger) tasks and did not result from a speed-accuracy trade off. Other video games used as training for different cognitive functions are *Tetris* (Goldstein et al., 1997), *Rise of Nation* (Basak, Boot, Voss, & Kramer, 2008), *Big Brain Academy* (Ackerman, Kanfer, & Calderwood, 2010), *Medal of Honor* (Belchior, 2007), and a variety of Atari's games such as *Breakout*, *Galaxian*, *Frogger*, *Kaboom*, *Ms. Pacman*, *Pengo*, and *Qix* (Dustman, Emmerson, Steinhaus, Shearer, & Dustman, 1992). While these studies reported how video games appear to be an effective means of enhancing reaction time, processing speed, executive function, and global cognition, it is obvious that the same video games cannot be used with individuals with cognitive impairments to deliver a cognitive rehabilitation. In video games developed for entertainment, for instance, one may be simultaneously engaged in memory tasks (e.g., spatial memory for the route to the enemy fortress, semantic memory for weapons at one's disposal or enemies still active), executive tasks (e.g., resource and weapon allocation, dual tasking), visual attention tasks (multiple object tracking, distractor rejection), visuomotor tasks (e.g., steering, piloting), and rapid object recognition (C S Green & Bavelier, 2008). Moreover, the interface and the stimuli could appear too much confusing and complicated for individuals with cognitive deficits. For this reason, researchers have designed training regimens for the purpose of brain/ cognitive training, specifically targeted for individuals with impairments that require a cognitive rehabilitation. Then, there is less attention to create interfaces with complicated animations, sounds and colors and more attention to the quality of the exercises proposed. The training is typically broken down into subdomains: as example semantic memory is being trained entirely separately from inhibition control, which, in turn, is trained separately from speed of processing. Now the exercises are specifically designed to address specific cognitive functions. In the case of the PRT most of the times the exercises are the digital and re-adapted version of exercises proposed in "Demenza. 100 esercizi di stimolazione cognitiva" (Bergamaschi et al., 2008). When we started developing the software we firstly decided to focus on individuals with dementia, and the paper and pencil exercises included in this book revealed to be effective in Italian population with dementia. In a randomized controlled trial 30 individuals with dementia were divided into three groups to explore the effective outcomes of a structured cognitive stimulation treatment in improving cognition and behavioral symptoms (Mapelli, Di Rosa, Nocita, & Sava, 2013). The experimental group received a cognitive stimulation treatment starting with initial personal, spatial, and temporal orientation sessions and proceeding with a structured stimulation for the cognitive domain using the exercises included in the book mentioned above. The placebo group daily performed a series of programmed activities: read and debate the newspaper, play bingo, sing, and take part in PET therapy, psychomotor stimulation and creative

workshops. The activities were changed every day and were adapted according to the degree of dementia. Both groups were involved in a 40-session program that ran daily over 8 weeks, for 1 h per session or 5 h weekly. Instead, the control group participants continued with the usual activities program at the nursing home while the group therapies were in progress. Results showed that at the global rating scale of dementia (CDR, Morris, 1993) the experimental group exhibited an improvement in terms of a decrease in dementia severity: the mean score on the CDR scale decreased significantly (p < 0.05), while that of the other two groups remained stable. The same pattern of results was observed for measure of cognitive function such as MMSE (Folstein, Folstein, & McHugh, 1975) and ENB 2 (Mondini, Mapelli, Vestri, Arcara, & Bisiacchi, 2011), and in measure of frequency of problem behaviors during dementia (Behave-AD, Reisberg, Auer, & Monteiro, 1996). The presence of a significant improvement only for the experimental group helps the data interpretation in terms of intervention specificity because the presence of a placebo group that did not show any significant improvement afterwards is strong evidence of the specificity of the cognitive stimulation treatment efficacy, and it is not attributable to similar social attention. In another study was tested the hypothesis that additional and repeated treatments of cognitive training using the paper and pencil exercises included in "Demenza. 100 esercizi di stimolazione cognitiva" would limit progressive cognitive decline in patients with AD and lead to improved cognition (Bergamaschi et al., 2013). Specifically, was examined the effectiveness of repeated cycles of cognitive training by comparing the cognitive performance of 16 patients with AD treated with cognitive training and cholinesterase inhibitors (ChEIs) (experimental group) with the performance of 16 patients treated with a non-specific cognitive treatment and ChEIs (control group). The patients in the two groups were administered a variety of neuropsychological tests measuring several cognitive functions (i.e. memory, language, reasoning, executive function, working memory and apraxia), activities of daily living, and depression. Results showed that patients who participated in the cognitive training intervention showed improvement in several cognitive measures and did not experience any decline on neuropsychological tests or in activities of daily living. On the contrary, patients who participated in non- specific activities at a Day Centre showed decline in both cognitive abilities and activities of daily living. Lastly, a study investigated the functional plasticity in individuals with Alzheimer disease analyzing the effect of a cognitive training (same exercises as before) on language-related ERP components. Eleven mild/moderate individual with Alzheimer underwent to a 5-week cognitive training (40 h). Before and after the training, evoked potentials were recorded from 26 scalp electrodes during a lexical decision task which required word/no-word discrimination. Stimuli included high- and low-frequency words and non-words, and the recognition potential (RP) together with the N400 have been analyzed and compared with those collected from a matched healthy control

group. Results comparing controls and patients before training showed a normal RP in AD patients with a clear peak over left occipito-temporal sites. In addition, controls exhibited a left anterior lateralization of N400 component to words and an inverted pattern for non-words, whereas an altered N400 with bilateral distribution at both word and non-word conditions was found in AD patients. After the cognitive training, AD patients did not show changes in the N400, but revealed a significant enhanced amplitude of RP to high-frequency words. This result demonstrates the possibility to actively stimulate and induce a neural reorganization even in a neurodegenerative disease like dementia.

Taken together the results of these studies allow to consider the exercise included in "Demenza. 100 esercizi di stimolazione cognitiva" a valid tool for cognitive training in patients with dementia. For this reason, we decided to develop a digital and adapted version of some of these exercises establishing a scientifically solid base for the PRT.

4.4. Flexibility

In origin the PRT was specifically designed for people with mild to moderate cognitive impairment. Indeed, in literature different studies examined and proved the positive effects on cognition of cognitive training with MCI, and Parkinson (Gates & Sachdev, 2014; Leung et al., 2015). Günther, Schäfer, Holzner & Kemmler (2003) tested a computer-assisted cognitive training program in 19 older persons with MCI. The participants were recruited from a residential home for older people. They had a memory complaint and performed 1 SD below normative values in memory tests. The program involved 14 training sessions and the effect of the training program was tested immediately after completion and five months later. The authors reported positive training effects on objective measures of episodic and working memory. Furthermore, the positive effect was maintained over the long term. In another study (Rozzini et al., 2007) the authors reported enduring effect in a one-year randomized study that compared 59 MCI patients receiving pharmacological therapy and cognitive training, pharmacological therapy only, or neither. The training program was applied in three blocks of 20 one-hour sessions. The group treated with pharmacological therapy and cognitive training improved their scores on memory and problem solving tasks as well as on the neuropsychiatric inventory. A study by Olazaran et al. (2004) reported positive effects of cognitive intervention in 72 people with AD and 12 persons with MCI. Participants were recruited from clinical units, and persons were identified as MCI on the basis of Flicker's criteria (equivalent to a GDS of 3). All patients attended a day hospital. Untreated patients attended the psychosocial program usually provided by the day hospital. Treated participants were enrolled in different cognitively demanding activities including list memorization during a one-year period. The study reported both an increase in cognition and a decrease in cognitive symptoms in those patients enrolled in the cognitive training

program relative to patients who attended the psychosocial program usually provided by the day hospital. Belleville et al (2006) developed a multi-factorial intervention program tailored to the needs of persons with MCI. The program was designed to improve episodic memory, a component that is shown to be impaired in MCI, by providing teaching on a number of episodic memory encoding strategies that rely on visual imagery, semantic knowledge and organization. Furthermore, the program included instruction on relaxation and on the impact of aging on cognition. A number of elements were implemented in the program to increase generalization, such as exercises with graded levels of difficulty, homework and specific instructions on how to use the strategies in real-life situations. Participants were invited to take part in eight weekly group sessions and they were tested with objective and subjective memory measures one week prior to and one week after the intervention. The study included 21 participants with MCI who took part in the training and eight participants with MCI who were included in a no-intervention control group. Groups of treated and untreated healthy older adults were also included in the program. The study reported a significant positive effect of the intervention on objective measures of episodic memory (delayed recall of word lists; face name association) in both healthy older adults and persons with MCI. Effects sizes for these intervention effects were large to medium. There was also a significant training effect on a subjective memory measure (memory questionnaire) and on well-being. In contrast, none of these measures improved in the no-intervention group. Another review analyzed the effects of cognitive training in Parkinson disease (Leung et al., 2015). The synthesis of outcomes found clinically meaningful improvements in overall cognition, as well as moderate to large effect sizes on measures of working memory, processing speed, and executive functions. In patients with Parkinson disease executive skills such as planning, cognitive flexibility, verbal fluency, and inhibitory control in addition to working memory type tasks have all been shown to be impaired (Kehagia, Barker, & Robbins, 2010; Robbins & Cools, 2014). That these functions are improved in response to cognitive training is encouraging, providing strong support for continuation of cognitive training trials in this population. Relying on this body of evidence we firstly decided to develop exercises addressing cognitive functions such as memory and attention. But progressively we adopted the idea of developing a wider software including exercises for other domains allowing cognitive rehabilitation for other categories of patients. Therefore, starting from a body of 6 exercises we developed a corpus of 35 different exercises addressing different cognitive functions. Considering the main cognitive function involved in every exercise we gathered 7 domains: attention, memory, language, logic reasoning, identification, orientation and motor control. The main advantage of a multi-domain software such as PRT is the flexibility: it allows to tailor the cognitive rehabilitation to the specific needs of every

different patient. It is possible to deliver every time a different training program addressing the specific cognitive functions impaired in each patient.

4.5. Usability, Feedbacks and other characteristics

I already discussed how the use of touch-screen technology solves the limits of traditional input devices. In order to make the software usable by a population with cognitive impairments a step further is needed: the development of an interface respecting specific design requirements. Fisk, Rogers, Charness, Czaja, & Sharit (2009) describe the principles for optimizing human-computer interactions in older people. The same principles are respected in the development of the PRT. The design guidelines can be grouped into the following categories: physical characteristics, which may be influenced by perceptual and movement control impairments; information organization; and more general conceptual issues. Regarding the physical characteristics, the first important guideline is to minimize the clutter. Clutter can be visual with too many display items in any one location, auditory with too many sounds to make sense out of, cognitive with too many things to keep in memory, and/or movement related with too many response items that are too small. Following this guideline, in the PRT there are the essential items displayed avoiding the use of unnecessary animations. The shapes of the items are elementary without using of complex scenes and confounding colors. There are only 3 sounds - for the feedback of tap gesture, for positive and for negative feedback – without using of background music. The text of the instructions is simple, direct and short. Secondly, it is important to ensure that screen characters and targets are conspicuous and accessible. For example, a font size less than 12 should be avoided; icons should be large enough to select easily; and auditory information should be presented at the proper pitch, frequency, and rate. In the PRT the items are never too small, in particular if they have to be "tapped" with finger, the text is largely displayed on the screen and the auditory information is adapted to the requested properties. Lastly, it has to be established an appropriate temporal constraint for carrying out commands ensuring that stimuli and menu durations are long enough to be able to carry out the commands.

Regarding the information organization, the guidelines require to optimize information organization within natural or consistent groupings, and to make frequent and important actions easily visible and accessible. In the PRT as example the exercises are divided in different cognitive domains, and each domain has his own and unique color present in the menu section. Moreover, it is always present and well visible a button for exiting from the exercises going back to the menu.

The most important general guidelines that has to be followed in creating a usable interface is the consistency. Location of items should be the same across screens and similar functions should act the same throughout the system. In the PRT, the location of the only two consistent button is always the same: bottom-right corner for "next" button (necessary for going to the next screen) and bottom-left

corner for "exit" button (necessary for going back to the menu). Moreover, these two buttons have always the same shape, size, and color: a green arrow for the "next" button and a red rectangle for the "exit" button. Furthermore, the sounds are consistent across the exercises as like the performance feedbacks. The system has to provide two different types of feedback: feedback about task completion and confirmation of activity, and feedback about the accuracy of the performance. Both are adequately provided by the PRT. After each tap a simple sound confirm that the system received the action of the user, and after each response auditory and visually feedback about the accuracy of performance are provided. This last type of feedback is essential during cognitive rehabilitation. It can be provided in a number of different ways: it can be immediate or delayed; on frequent basis (after each step in a practice task) or an infrequent basis (at the end of the practice task or the training session); extensive (e.g., providing the conceptual basis for why an action is wrong and suggesting the correct answer) or relatively brief (e.g., providing the number of wrong answers). To the different type of feedback correspond different rehabilitation techniques. The one with proved efficacy in particularly in the treatment of aphasia and amnesia is the *errorless learning* approach. In the *errorless learning* approach, the basic assumption is that errors that are produced during learning interfere with the correct responses (Baddeley, 1992). There is evidence that these errors are stored in memory through intact implicit learning. Normally, these errors are corrected by explicit memory processes, but since the latter are impaired in amnesic subjects, errors may be actually consolidated in this patient group. This hypothesis was explored in a study comparing trial-and-error learning (resulting in errors during learning) with a condition in which the making of errors was prevented (i.e., *errorless learning*). The memory performance in the *errorless learning* condition was higher than during the trial-and- error learning (Baddeley & Wilson, 1994). The effects of *errorless learning* have been investigated in different reviews (Kessels & de Haan, 2003; Middleton & Schwartz, 2012): the elimination or reduction of incorrect or inappropriate responses during training facilitates memory performance. Moreover, *errorless learning* offers one important parameter which may be very beneficial for people with cognitive impairments: as errors are avoided or minimized, participants have the opportunity to experience success at every stage of the learning process. In the PRT, after each answer auditoryily and visually feedback consistent with the accuracy of performance are provided. Each exercise is constituted by different levels of difficulty. In order to minimize the errors every exercise starts from a very easy level. Thus, participants can experience success reducing the sense of frustration and improving the motivation. Typically, the parameters that vary in order to increase the difficulties of exercises are the number of distractors, the presentation time of the stimuli on the screen and the type of stimuli (e.g, disyllabic vs trisyllabic words). If the response is not correct, the patient has the possibility to retry the same level up to three times. Thereafter the exercise ends

in order to avoid the repetition of the same error improving the sense of frustration in the patient and the software automatically goes back to the menu of the exercise selection.

Another important features of the PRT is that in some exercises the patient has the possibility to directly decide some parameters (e.g., the figure target) and thus he can feel to be able to manage his own rehabilitation.

The PRT consists of many different easy stimuli. This is important in order to not bore the user. Moreover, the stimuli are randomly generated and positioned on the screen. Thus, it is avoided an automatic learning of the correct answer or the correct position of the target stimulus: every time the patient has to maintain high concentration and to find the new correct solution.

Finally, after each response the system automatically records all the relevant information in a local database associated with an ID of the user. In addition to ID and date, depending on the exercise, are typically recorded the current level, the reaction times, the omission, the number of attempts and the wrong answer.

4.6. The exercises

The Padua Rehabilitation Tool consist of 35 exercises divided into 7 cognitive domains: attention, memory, language, logic reasoning, identification, orientation and motor control. Follow a brief description of the exercises developed grouped by domain (see Appendix 1 for screenshots of the various exercises).

4.6.1. Attention

The Attention domain includes 4 exercises:

- *Quanti (how many?)* the patient has to select a target image choosing among a pencil, a flower, an apple or a light bulb. Then, he has to count the occurrences of the selected item between a number of distractors in the screen. There are two version of these exercise that differ for the method for going to the response screen: "libero", the patient has all the time he wants to count the object and then he can tap the "next" button to go further; "a tempo", a fixed amount of time is set for each level, after which automatically the system moves to the response screen. There are 6 difficulty's levels: the number of total stimuli increase going from 9 to 72.

- *Go/No go*: the patient has to tap the screen (in any position) once a target stimulus is presented. At the beginning of the exercises can be set some parameters. (1) Shape of stimuli: "square vs circle" or "x vs +"; (2) Number of stimuli to be presented; (3) Immediate feedback: an immediate auditory feedback congruent with the accuracy after each tap. If it is not selected the feedback is given at the end of the exercise. (4) time of presentation of each stimulus: there are 5 possibilities (400ms, 800ms, 1sec, 2sec, 3sec); (5) colors: if it is selected, the patient has

to discriminate also the color of the stimulus. Indeed, the set of wrong stimuli can include colored images, including the same shape of target but with a different color.

- *Detect*: at the beginning of this exercise the patient has to select a blue figure choosing among a square, a circle, a triangle or a pentagon. Then, as fast as possible he has to tap the blue figure selected among a number of distractors presented on the screen. There are 3 different sub-parts of this exercise in each one the number of distractors is progressively raised (from 1 to 11): (1) the stimuli are all in blue; (2) the distractors can be of different colors but the target is presented only in blue; (3) both the distractors and the target can be of different colors.

- *TMT*: this is a revised version of the Trail Making Test. As like the neuropsychological test it is divided in two parts. In the first, patient has to draw a line with the finger connecting consecutive numbers. In the second part, patient has to draw a similar line, connecting alternating numbers and letters in sequence (i.e., 1-A-2-B and so on). For each part there are three levels increasing the number of point to connect (from 4 to 12).

4.6.2.   Memory

The Memory domain include 7 exercises:

- *Interferenza (Interference)*: the patient has to memorize a sequence of three letters. After a confounding task he has to retrieve the sequence tapping the correct letters. The interfering task consist in reading aloud an increasing number of short words presented on the screen. There are 2 parameters that can be set: (1) time presentation of the sequence to be memorized (3sec, 6sec, 8sec); (2) the number of distractor letters presented in the response screen (2, 4, 7). In each level is increased the number of letters to read aloud (from 1 to 10).

- *Digitspan*: the patient has to memorize a sequence of digits presented one by one on the screen. The minimum number of digits to memorize is 2 and the maximum is 8. In the early phase (up to 5 digits) the exercise is divided in two phases: in the first, the response screen includes the number of digits to be memorize plus one distractor, in the second phase it includes all the numbers from 1 to 9.

- *Cosa era (What was?)*: in this exercise the patient has to look a static scene presented on the screen trying to memorize all the object presented. After a pre-selected delay of time, the scene disappears and a set of objects is visualized: the patient has to tap only on the objects that were presented in the scene. There are two different scenes, and respectively 4 and 7 object to recognize. Moreover, the difficulty of the exercise can be varied choosing the duration time of the scene on the screen (5sec, 10sec, 20sec).

- *Che oggetto era? (What was the object?)*: in this exercise the patient has to read and memorize some words presented one by one on the screen. Later, are presented on the screen some

pictures. The patient has to tap only on the pictures that match with the words he has read. The difficulty of this exercise changes increasing the number of words to read and memorize, and increasing the number of pictures presented.

- *Memory:* this is a version of the classic memory game. A set of cards is randomly placed face down on the screen. The patient tap cards two at a time. If the pictures on the cards match, the pair is kept turned on the screen. Pairs that do not match are turned back until all the pairs are matched. There are 5 levels with an increasing number of pairs to found: 2, 3, 4, 5, 6.

- *Memory – Sound*: this exercise is very similar to the previous one. Instead of pairs of pictures, the patient has to match pairs of sounds.

- *Pattern*: this exercise is similar to a Corsi Span Task (1973). On the screen is presented a grid. One by one some of the cells of this grid are enlightened. The patient has to memorize and repeat the sequence of the cells enlightened. There are 21 levels, and the difficulty is varied changing two parameters: the length of sequence to memorize (from 4 to 6 cells) and the dimension of the grid (from 3x3 to 6x6).

4.6.3.   Language

The Language domain consists of 9 exercises:

- *Ordine alfabetico (Alphabetical order)*: in this exercise the patient has to alphabetize the letters or the words presented. At the beginning it is possible to decide if use an ascending (A-Z) or descending (Z-A) order. The exercise is divided into 5 sub-parts changing the type of stimuli presented: (1) letters; (2) disyllabic words; (3) trisyllabic words; (4) disyllabic words, including word with same initial; (5) trisyllabic words, including words with same initial. Moreover, in each part there are different levels of difficulty increasing the number of stimuli to alphabetize (2, 3, 4, 6, 8 ,12 ,14).

- *Completa la parola (Complete the word)*: the patient has to complete compound words. On the left-side of the screen is presented the first stem. The patient has to choose between the words presented on the right-side of the screen which one complete correctly forming a compound word. There are 6 levels of difficulty with an increasing number of confounding words on the right-side of the screen (from 2 to 7). For each level there are three different trials.

- *Crea la parola (Create the word)*: similar to the previous exercise, the patient has to choose the correct syllable forming a sense word together with the syllable presented on the left-side of the screen. The exercise is divided in two parts: (1) the patient has to form a disyllabic word; (2) the patient has to form a disyllabic words and then he has to choose an additional

syllable forming a trisyllabic word. For each part, there are different levels of difficulty increasing the number of confounding syllable.

- *Sillabe (Syllables)*: this exercise is divided in two parts. The first one is the same of the first part of the previous exercise: the patient has to form a disyllabic word choosing among several stimuli the correct second syllable. There are 6 levels that vary for the number of stimuli presented (from 2 to 7). In the second part of the exercise a target syllable is presented on top-side of the screen. Above there are different syllables and the patient has to choose the correct ones that form a disyllabic word with the target one. There are 6 levels with an increasing number of stimuli presented (from 4 to 14).

- *Intruso (Intruder)*: the patient has to find the unrelated word in a list of 4 words. In this exercises there are not different difficulty levels: every time are presented all the 16 lists of words and it is recorded the total number of errors.

- *L'Iniziale (Initial)*: on the screen are presented some pictures and some letters. The patient has to match each picture with his initial. In the first part there is only one picture for letter; in the second part there are two picture for the same letter. The number of pictures presented range from 2 to 8.

- *L'Iniziale 2 (Initial 2)*: similar to the previous one, on the screen are presented some pictures and some letters. The patient has to tap on the only letter that is not the initial of the pictures presented. There are 7 levels with an increasing number of pictures ranging from 1 to 7. For each level there are three different trials.

- *Sinonimi (Synonyms)*: in this exercise on the left-side of the screen is presented a target word and the patient has to choose his synonymous among the different words presented on the right-side of the screen. The number of words listed on the right-side of the screen increase ranging from 2 to 7. For each level there are three different trials.

- *Contrari (Antonyms)*: this exercise is similar to the previous one. The only difference is that the patient has to choose the antonymous instead of the synonymous.

4.6.4. Logic Reasoning

The Logic Reasoning domain consist of 3 exercises:

- *Denaro (Money)*: in this exercises are randomly presented on the screen pictures of banknotes, of coin, or both (Euro currency). The patient has to count the money and report the total amount. There are 5 levels of difficulty. In each level a new picture is presented increasing the difficulty of the addition operation.

- *Stime di denaro (Money estimates)*: in this exercise patient has to make a price estimation of the product showed on the screen. For each trial he has to choose the best estimation among

three alternatives. The difficulty of this exercises vary changing the type of product to estimate and the format of the alternatives: everyday life products (such as coffee, newspaper, milk, ice-cream…) Vs unusual products (such as car, flight, salary, one-night in hotel…); price in digits (e.g., "1.20 €") Vs adverbs of quantity (e.g. "meno di 200 euro")

- *Sequenze (Sequences)*: in this exercise are presented on the screen in random position the parts of a comic strip. The patient has to re-create the correct sequence. There are 5 levels, with an increasing number of parts that complete the story of the comic strip, ranging from 2 to 6.

4.6.5. Identification

The Identification domain consists of 4 exercises:

- *Suoni (Sounds)*: the patient has to identify the sound played. He has 4 alternatives, and before tap on one of these, he can listen again the sound. There are no levels of difficulty and every time he has to recognize 20 random different sounds. At the beginning of the exercise it is possible to decide how the alternatives are presented: pictures or text.

- *Oggetti – 1 (Objects 1)*: in this exercise the patient has to read a word presented on top-side of the screen and then identify the related picture. There are 5 levels: the pictures presented can be 3, 4, 6, 8, 12. For every level there are three trials.

- *Oggetti – 2 (Objects 2)*: this exercise is similar to the previous one, but inverted. The patient has to identify a picture choosing the correct name among few alternatives. There are 4 levels, with an increasing number of alternative words (3, 4 ,6 ,8).

- *Rotazioni (Mental rotation)*: in this exercise a target stimulus is presented and the patient has to identify which one of the alternatives is the same stimulus rotated. The difficulty varies changing two parameters: the number of distractors, and the similarity between distractors and target.

4.6.6. Orientation

The Orientation domain consists of 3 exercises:

- *Orario (Clock)*: the patient has to tap on the clock face that represent the time presented. In the first part of the exercise the time is presented only on 12-hour clock system (e.g., "09:10", "3:50"); in the second part the time is presented in 24-hour clock system (e.g., "21:10", "15:50"). For both of the parts there are 3 levels where it is increased the number of clock face stimuli (2, 3, 4).

- *Cerca il gatto (Find the cat)*: in this exercise is presented a full-screen picture of a room with several cats. The patient has to tap on the cat specified by the instructions (e.g. "Tocca il gatto a sinistra della vasca"). There are 3 levels: in the first one there are 6 cats all identical; in the

second one there are 9 cats different for color (black, grey or white); in the third one there are 12 cats different for color (black, grey or white) and size ("small" Vs "big").

- *Metti le lancette (Put the hands in the clock)*: in this exercise a clock face without hands is presented. The patient has to put the hands of the clock on the correct numbers marking the time presented at the top-side of the screen. As like the "Orario" exercise, there are two parts: in the first part the time is presented only on 12-hour clock system (e.g., "09:10", "3:50"); in the second part the time is presented in 24-hour clock system (e.g., "21:10", "15:50").

4.6.7. Motor Control

The Motor Control domain consists of 5 exercises:

- *Snake*: in this exercise the patient has to drag a "snake" (using the pan gesture) towards red dots avoiding the walls. There are 7 levels: the numbers and the complexity of walls increase. In each level, 5 dots are randomly presented one by one.

- *Snake 2*: this exercise is a union of "TMT" and "Snake". The patient has to drag a "snake" towards consecutive numbers (from 1 to 12). There are 5 levels: the numbers and the complexity of walls increase.

- *Bersaglio (Target)*: the patient has to hit a target closely as possible to his center in order to make points. The target appears in a random position at every trial and it consists of a circle with 4 concentric areas: at each area correspond a score (5, 10, 15, 20); 10 points are subtracted in case of missing target. There are 4 levels: the time presentation of the target on the screen is progressively reduced (4sec, 3sec, 2sec, 1sec).

- *Bersaglio 2 (Target 2)*: this exercise is similar to the previous one. The patient has to hit a target closely as possible to his center. This time are also presented distractor targets of different shape. The score system is equal as before and in case of hitting a distractor the same amount of point is subtracted (-5, -10, -15, -20). There are 4 levels: the number of distractor targets is progressively increased (1, 2, 3, 4). All the stimuli appear in a random position at every trial.

- *Completa la forma (Complete the picture)*: this exercise is similar to a puzzle. The patient has to drag the pieces of a picture within a frame. In the second part, the pieces of picture need also to be correctly rotated. For each part, there are 3 different puzzles with an increasing number of pieces (2, 3, 4).

Chapter_5 Efficacy evaluation of PRT in patients with dementia

After the developing phase of the Padua Rehabilitation and the beta testing we focused our attention on testing the efficacy and the effects of a training with PRT. As mentioned before the software was principally developed for people with dementia, then our main effort was focused on the study of the efficacy of this software with this population. In this Chapter are reported the method, and the results of a training using PRT in an Italian population with dementia.

Introduction

The world's population is ageing: the world's older population currently comprises nearly 900 million people. Most live in what are currently relatively poor countries. Improvements in health care in the past century have contributed to people living longer and healthier lives. Mortality rates among older people are falling, and life expectancy from age 60 continues to increase in all world regions, with no upper limit in sight (population ageing or the "demographic transition") (World Health Organization, 2012). In Italy, since 1974 the life expectancy is increased of 10 years and today it is about 80 years old for male and 85 for women. Moreover, the percentage of population over 65 years old is 22% and increase of about 0.2-0.3% every year (I.Stat, 2016). As people live longer, so chronic diseases become more prevalent, a trend exacerbated by changes towards lifestyles and behaviors that predispose towards them. However, this has also resulted in an increase in the number of people with dementia. Prevalence and incidence projections indicate that the number of people with dementia will continue to grow, particularly among the oldest old, and countries in demographic transition will experience the greatest growth. The total number of people with dementia worldwide in 2015 is estimated at 46.8 million and is projected to nearly double every 20 years, to 74.7 million in 2030 and 131.5 million in 2050. The prevalence rates for all those aged 60+ range from 8.67% and 8.41% respectively in North Africa/Middle East and East Asia, going through 6.7 in North America and Western Europe, to 4.6% in Central Europe (Prince et al., 2015). The total number of new cases of dementia each year worldwide is nearly 9.9 million, implying one new case every 3.2 seconds. Surely, this enormous numbers are connected to the incredible cost of dementia: the global societal economic cost of dementia in 2015 was estimated in US$ 818 billion. Moreover, there is a disjunction between the global distribution of prevalence, 58% of which is accounted for by people with dementia living in lower-middle income countries (e.g., India, Tunisia, Ghana), and costs, 87% of which are incurred in high-income countries (e.g., Italy, France, United States). The uneven distribution of global costs is even more striking when stratified according to G7: 62% of worldwide costs incurred by just seven nations. While these numbers and statistics are daunting, the impact on those with the illness and on their caregivers and families is extreme – medically, psychologically and emotionally. The behavioral

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and psychological symptoms linked to dementia profoundly affect the quality of life of people with dementia and their caregivers. Thus, the challenges to governments to respond to the growing numbers of people with dementia are substantial: a broad public health approach is needed to improve the care and quality of life of people with dementia and family caregivers.

Firstly, the attention of some researchers was focused into the possibility of prevent the onset of dementia thanks to cognitive training in older adults. Valenzuela and Sachdev (Valenzuela & Sachdev, 2009) in a review concluded that suggests that a discrete dose of cognitive training in the order of 2–3 months may have long-lasting and persistent protective effects on cognition over a number of years in healthy older individuals. They reported an overall integrated effect size of 1.07 (CI: 0.32–1.83). In clinical terms, this effect approximates a relative improvement of 1.2/2.6 points in the MMSE, or 4.1/9.9 ADAS-Cog points, when extrapolated to a community-based sample of either older cognitively intact individuals or those with Mild Cognitive Impairment (MCI), respectively. The largest trial included in the review has been the ACTIVE study (Ball et al., 2002), which examined the effect of 10 sessions of cognitive training on 2,832 healthy older individuals divided into three different intervention groups: memory training, reasoning training, and processing speed training. Each intervention improved cognitive ability in the targeted area 2 years later. Moreover, a 5-year follow-up to the ACTIVE study has been reported with change in IADLs used as a main outcome measure (Willis et al., 2006). Reasoning training specifically protected against functional decline over this extended follow-up period compared with any of the other interventions or the control wait-and-see condition. In another study, Mahncke et al. (2006) conducted a randomized controlled trial to evaluate the magnitudes of the effects resulting from a computer based cognitive training, as compared with active control and no-contact control groups. A total of 182 participants consented and were randomized into the study, with 62 in the experimental training (ET) group, 61 in the active control (AC) group, and 59 in the no-contact control (NCC) group. The AC group watched and listened to DVD-based educational lectures and other programs by using the DVD player capability of their computers. Results showed how use of the ET program for 8–10 weeks resulted in a significant increase in task-specific performance, indicating that participants were able to learn the exercises and intensive practice on these exercises yielded improvements on them. The Authors reported a generalization effect demonstrated in the improvements seen in non-trained, standardized neuropsychological measures of memory functions and a maintenance of results over a 3-month period after the completion of training during which no further training activities occurred. While these studies investigated the possibility of prevent the onset of dementia thanks to cognitive training in older adults, other researchers focused the attention directly on cognitive training in patient with dementia. The results reported in literature are different and contrasting. For example, the main

results of a review (Bahar-Fuchs et al., 2013) showed no positive or adverse effects of cognitive training. The finding of no adverse effects of cognitive training is relevant in light of proposals from previous commentators (Small et al., 1997) that cognitive training may have a negative impact, particularly on mood. However, this review includes only randomized controlled trials, and thus it not considers all the high-quality non randomized trials. Moreover, the Authors not included several RCTs of cognition-based interventions either did not meet their definitions of cognitive training and cognitive rehabilitation or described multi-component interventions. On the other hand, Sitzer, Twamley and Jeste (2006) concluded their review of literature positing that cognitive training evidenced promise in the treatment of AD, with primarily medium effect sizes for learning, memory, executive functions, activities of daily living, general cognitive problems, depression, and self-rated general functioning. Furthermore, differential effects of cognitive training were observed when compared with different control groups. Stronger effects were observed for investigations comparing cognitive training to wait-list controls (Koltai et al., 2001; M P Quayhagen et al., 2000; Requena, Maestú, Campo, Fernández, & Ortiz, 2006; Zanetti et al., 2001) rather than to attention-placebo controls (Bach, Bach, Bohmer, Fruhwald, & Grilc, 1995; Cahn-Weiner et al., 2003; Davis et al., 2001). In a study, the Authors evaluated the efficacy of a cognitive program on memory and functional performance of mildly impaired Alzheimer disease patients receiving a cholinesterase inhibitor (Loewenstein et al., 2004). Twenty-five participants in the cognitive rehabilitation condition participated in two 45-minute sessions twice per week for 24 total sessions. The cognitive rehabilitation training included face–name association tasks, object recall training, functional tasks (e.g., making change, paying bills), orientation to time and place, visuomotor speed of processing, and the use of a memory notebook. Nineteen participants in the control condition had equivalent therapist contact and number of sessions, which consisted of interactive computer games involving memory, concentration, and problem-solving skills. The results showed how compared with the control condition, participants in the cognitive training demonstrated improved performance on tasks that were similar to those used in training. Gains in recall of face–name associations, orientation, cognitive processing speed, and specific functional tasks were present post-intervention and also at a 3-month follow-up. Other evidences supporting the positive effects of cognitive training in reducing the progressive cognitive decline in patients with dementia and leading to improved cognition come from the study on Italian population that I already discussed in paragraph 4.3 (Bergamaschi et al., 2013; Mapelli et al., 2013; Spironelli, Bergamaschi, Mondini, Villani, & Angrilli, 2013). As I said before the Padua Rehabilitation Tool (PRT) is mainly inspired by the paper & pencil exercises used in these studies.

Moreover, other important input to this study comes from the evidence supporting the effectiveness of touch screen as new technology for rehabilitation (see Chapter 2).

Thus, we decided to put together the effectiveness of a cognitive training program with the effectiveness of a technology. The result is the development of a completely new and innovative cognitive training for patients with dementia using the Padua Rehabilitation Tool. The aim of this study is to examine the effects of such training on both cognitive and neuropsychiatric measures. Considering the previous results of similar tools, we hypothesize to find comparable effects on patients that used the PRT and those who were involved in traditional paper and pencil training. We hypothesize that the use of touch screen does not lead to higher cognitive improvement if compared to paper and pencil rehabilitation but at least at same results. Indeed, the advantages of using this technology rely on usability, portability, precision and motivation aspects rather than in efficacy.

Method

Participants

A total of 40 participants with diagnosis of dementia (Mean Age = 80.8, SD = 8.8, 12 males) were recruited in three different care center in Italy: Centro Residenziale Anziani in Cittadella (Padua), Centro Servizi per Anziani in Monselice (Padua), and Casa di Cura Figlie di San Camillo (Cremona). They were evaluated for their eligibility by the neurologist and neuropsychologist of the respective care center. Inclusion criteria included subjects at stage 1 or 2 on the Clinical Dementia Rating Scale (CDR) (Morris, 1993), with a Mini Mental Score Examination score (MMSE) (Folstein et al., 1975) ranged between 14 and 25. They were able to communicate and understand verbal and written language and physically able to participate in a meaningful assessment and a rehabilitation program. Subjects who suffered from a learning disability or severe psychiatric or internal disorders, such as schizophrenia or alcoholism, were excluded. The patients were randomly assigned to the three treatment conditions: (1) no treatment, (2) PRT, (3) traditional paper and pencil (P&P). The groups were not significantly different for age ($F_{2,37}$=.665 p=.52), education ($F_{2,37}$=1.857 p=.17) and MMSE scores ($F_{2,37}$=1.59 p=.217). There was no significantly difference between care centers for MMSE scores ($F_{2,37}$=.259 p=.772), while age ($F_{2,37}$=6.1 p=.005) and education ($F_{2,37}$=27.4 p<.01) were significantly different: patients in "Casa di Cura Figlie di San Camillo" were younger and with more years of education compared to the other two centers. Refer to **Table 6** for group and total sample descriptive statistics of age, education and MMSE score. In accordance with the policies set from each care center, informed content was obtained for all participants before their participation in the study.

Outcome Measures

All patients were assessed before treatment (t0) and after treatment (t1). Thirty-four out of 40 were also assessed one month after the end of treatment (t2): because of the policy of one of the care centers 6 patients were not assessed at the follow-up. We decided to use both cognitive and neuropsychiatric measures. The cognitive assessment consisted on the largely used Mini Mental State Examination (MMSE) with the scores adjusted for age and education as proposed by Magni et al. (1996). MMSE it is commonly used to screen dementia and to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time. It takes between 5 and 10 minutes and includes questions about orientation to time and place, registration, attention and calculation, recall, language, repetition, and complex command. The maximum score is 30 and correspond to a normal cognitive functioning.

Table 6 Descriptive statistics of age, education and MMSE before intervention

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min	Max
						Lower Bound	Upper Bound		
AGE	no treatment	11	82,36	7,325	2,209	77,443	87,285	68,00	93,00
	PRT	18	79,06	9,759	2,300	74,203	83,908	62,00	95,00
	P&P	11	82,27	8,810	2,656	76,354	88,191	64,00	91,00
	Total	40	80,85	8,825	1,395	78,028	83,672	62,00	95,00
EDUCATION	no treatment	11	6,36	3,802	1,146	3,809	8,918	1,00	13,00
	PRT	18	8,61	5,606	1,321	5,823	11,399	3,00	19,00
	P&P	11	5,45	2,945	0,888	3,476	7,433	2,00	12,00
	Total	40	7,13	4,648	0,735	5,639	8,611	1,00	19,00
MMSE	no treatment	11	20,87	1,778	0,536	19,678	22,067	17,80	24,00
	PRT	18	22,16	1,741	0,410	21,290	23,021	18,40	24,70
	P&P	11	21,94	2,328	0,702	20,372	23,500	18,00	24,40
	Total	40	21,74	1,956	0,309	21,117	22,368	17,80	24,70

PRT, Padua Rehabilitation Tool; P&P, Paper & Pencil; MMSE, Mini Mental State Examination

Cognitive functions were also evaluated with the Alzheimer's Disease Assessment Scale (ADAS) (Rosen, Mohs, & Davis, 1984). It was designed specifically to evaluate the severity of cognitive and non-cognitive symptoms in patients with dementia of the Alzheimer type (AD). Only the cognitive section was used in this study which consists of 11 items, 8 performance based and 3 ratings of language impairment, measuring the disturbances of memory, language, praxis, attention and other cognitive abilities which are often referred to as the core symptoms of Alzheimer disease. Most of these items have a score from 0 (no deficit) to 5 (severe deficit). The maximum score is 70 indicating a severe deficit in all the items.

Considering the evidences supporting that almost 88% of the AD subjects reports one or multiple neuropsychiatric symptoms (Lyketsos et al., 2001; Mega, Cummings, Fiorello, & Gornbein, 1996) we decided to assess also this dimension. Thus, we used the Neuropsychiatric Inventory (NPI) (Cummings, 1997). It was developed to assess dementia-related behavioral symptoms and it examine 12 sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time

behavioral disturbances and appetite and eating abnormalities. The NPI is administrated to caregivers of dementia patients. A screening question is asked about each sub-domain. If the responses to these questions indicate that the patient has problems with a particular sub-domain of behavior, the caregiver is only then asked all the questions about that domain, rating the frequency of the symptoms on a 4-point scale, their severity on a 3-point scale, and the distress the symptom causes them on a 5-point scale. The domain total score is the product of the frequency score multiplied by the severity score for that behavioral domain. A NPI total score is obtained by summing all the individual domain total scores (NPI FxS). The second total score is obtained summing all the distress scores (NPI D).

We also decided to assess specifically the symptom of mayor depression using the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos, Abrams, Young, & Shamoian, 1988). It was specifically developed to assess signs and symptoms of major depression in patients with dementia. Because some of these patients may give unreliable reports, the CSDD uses a comprehensive interviewing approach that derives information from the patient and the informant. Information is elicited through two semi-structured interviews; an interview with an informant and an interview with the patient. Based on these interviews, the interviewer can score the CSDD by assigning a score to each item of the. The interviews focus on depressive symptoms and signs occurring during the week preceding the interview. The final ratings of the CSDD items represent the rater's clinical impression rather than the responses of the informant or the patient. Each item is rated for severity on a scale of 0-2 (0=absent, 1=mild or intermittent, 2=severe). The item scores are: scores above 10 indicate a probable major depression; scores above 18 indicate a definite major depression; scores below 6 are associated with absence of significant depressive symptoms.

Intervention

After a formal assessment, within each care center the patients were randomly assigned into no treatment, P&P and PRT groups. The P&P and the PRT groups received a 5 weeks individual intervention. Four times a week (20 sessions) for ~1h participants in the P&P group received a classic cognitive interventions using paper and pencil exercises; for the same amount of time patients in the PRT used the software together with a clinician. The choice of the session exercises for both groups was taken by the clinician, based on the needs and the characteristics of each patient.

The patients of the no treatment group were daily involved in a series of activities normally programmed by the care centers: read and debate the newspaper, watch television, play cards, sing, and take part in psychomotor stimulation and creative workshops. They were assessed after 5 weeks and again after 9 weeks as like the patients in the other groups.

Statistics

Given the structure of the observed data, we used a mixed-effects model approach. The most important advantage of mixed-effects models is that they allow the researcher to simultaneously consider all factors that potentially contribute to the understanding of the structure of the data (Baayen, Davidson, & Bates, 2008). These factors comprise not only the standard fixed-effects factors controlled by the experimenter but also the random-effects factors, in other words, factors whose levels are drawn at random from a population. Furthermore, multiple responses from the same subject cannot be regarded as independent from each other, thus violating the independence assumptions of linear models (Winter, 2013): every person has a slightly different cognitive profile, and this is going to be an idiosyncratic factor that affects all responses from the same subject, thus rendering these different responses inter-dependent rather than independent. The best way to deal with this situation is to add a random effect for patient. This allows to resolve this non-independence by assuming a different "baseline" for each subject. Basically, the mixed effect model allows to unpack the error part of the classic formula of a model adding complexity to it: part of the "error" can be explained by the intra-subject variability (the random effect). We are still interested in looking at the fixed-effects but using mixed models they are estimated considering the different baseline for each subject. In our analyses the fixed-effects were the "time", "group" and their interaction; as random effects we used a random intercept for each patient. For each dependent variable (MMSE, ADAS, NPI FxS, NPI D, CSDD) we run a model using the following general formula:

$$Dependent\ Var. = time + group + time{:}group + (1|id)$$

where time:group represent the interaction and (1|id) the random intercept for each subject. Type II Wald chisquare tests were run for examining the fixed-effects. Post-hoc comparisons with FDR controlling procedure (Benjamini & Hochberg, 1995) were also run for examining more in specific the multiple contrasts. All the analyses were completed using RStudio versions 0.99.903 (Rs. Team, 2015) with R version 3.3.0 (R. C. Team, 2016) and the packages *lme4* (Bates, Mächler, Bolker, & Walker, 2015), *lmerTest* (Kuznetsova, Brockhoff, & Christensen, 2015), *effects* (Fox, 2003), *lsmeans* (Lenth, 2016), and *xlsx* (Dragulescu, 2014). In the analyses relative to the neuropsychiatric measures 4 subjects (all in the PRT group) were excluded from t2 because of unexpected events occurred between t1 and t2. These patients were hospitalized because of bone fractures or because a worsening of medical conditions: legitimately this provoked a worsening in neuropsychiatric symptoms such as depression and apathy. The cognitive functioning was not affected by the hospitalization.

Results

The results are presented separated for each dependent variable.

MMSE

The results show a significant effect of time ($\chi^2(2) = 7.07$, $p=.029$), group ($\chi^2(2) = 14.85$, $p<.001$) and a significant effect of the interaction between time and group ($\chi^2(4)=18.71$, $p<.001$). The post-hoc comparisons show how groups were not different at t0, but there is a significant difference at t1 between no treatment and PRT groups ($t_{70.92}=-3.163$, $p<.01$) maintained at t2 ($t_{80.23}=-4.306$, $p<.001$), and no treatment and P&P groups ($t_{70.92}=-3.061$, $p=.01$) maintained at t2 ($t_{70.92}=-4.611$, $p<.001$). Furthermore, there is a significant improvement from t0 to t1 ($t_{74.51}=-2.377$, $p=.03$) and from t0 to t2 ($t_{77.96}=-2.430$, $p=.03$) in PRT group. The same significant improvements were observed in the P&P group (t0-t1: $t_{74.51}=-2.484$, $p=.02$; t0-t2: $t_{74.51}=-3.312$, $p<.01$). Refer to **Figure 6** for a plot of the effects with confidence bounds.
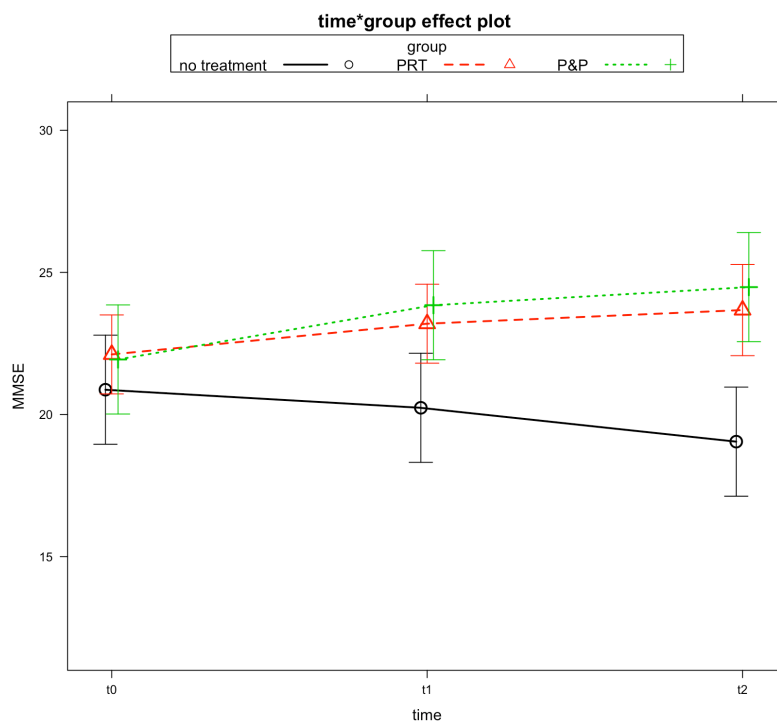
Figure 6 *Effect plot with confidence bounds in MMSE. (PRT, Padua Rehabilitation Tool; P&P, Paper & Pencil)*

ADAS (Cognitive)

The results show a significant effect of time ($\chi^2(2) =19.96$, $p<.001$) and group ($\chi^2(2) =15.36$, $p<.001$) but no effects of the interaction ($\chi^2(4) =2.89$, $p=.57$). Indeed, groups were not paired and controlled for the ADAS score: at t0, no treatment group patients had score significantly higher than PRT group ($t_{52.20}=3.221$, $p<.01$) and P&P group ($t_{52.20}=2.584$, $p=.01$). The same difference is maintained at t1 and t2. As shown in **Figure 7** individually all groups exhibit a trend of improvement (low scores) at t1, but only in the PRT this trend is maintained at t2 with a significant difference between t0 and t2 ($t_{75.73}=3.623$, $p<.01$).
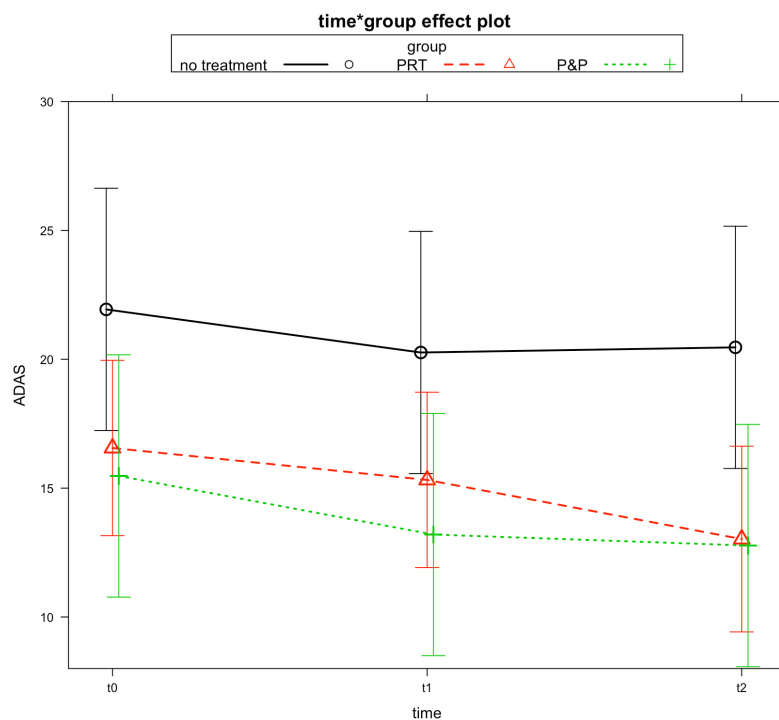
***Figure 7** Effect plot with confidence bounds in ADAS. (PRT, Padua Rehabilitation Tool; P&P, Paper & Pencil)*

NPI Frequency x Severity

The results show a significant effect of time ($\chi^2(2)$=12.13, $p<.01$) and a significant effect of the interaction between time and group ($\chi^2(4)$ =11.31, $p=.02$). Post-hoc comparisons show a significant difference at t0 only between no treatment and PRT groups ($t_{82.11}$=-2.555, $p=.03$) that became no longer significant at t1 ($t_{82.11}$=-0.066, $p=.94$). Indeed, the PRT group showed a significant improvement between t0 and t1 ($t_{69.44}$=3.550, $p<.01$), maintained at t2 ($t_{78.42}$=2.323, $p=.03$). The same significant improvement overtime was observed in the P&P group (t0-t1: $t_{69.44}$=2.180, $p=.04$; t0-t2: $t_{69.44}$=2.471, $p=.04$). **Figure 8** shows how the no treatment group has a worsening trend across time while PRT and P&P groups revealed an opposite one.
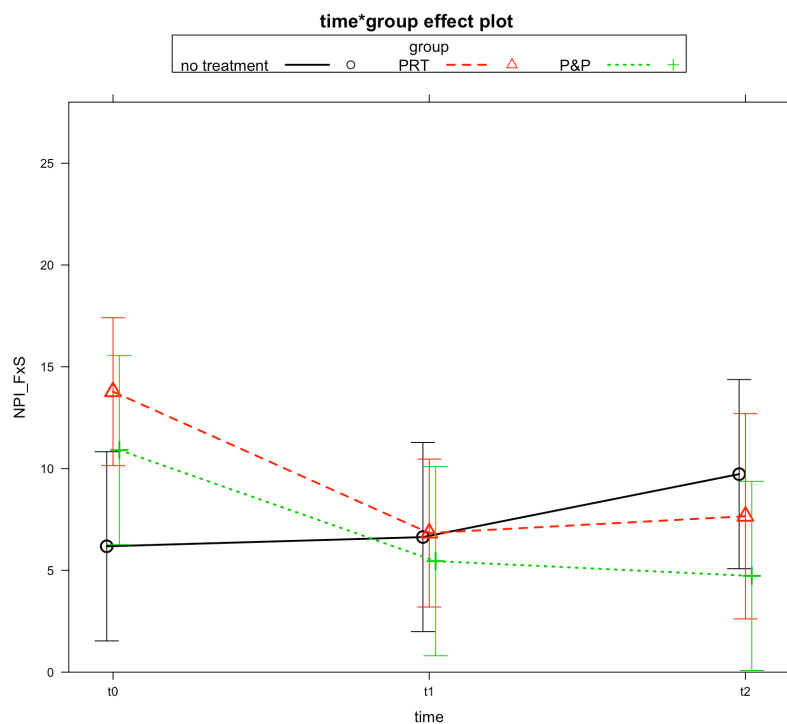
Figure 8 *Effect plot with confidence bounds in NPI Frequence x Severity. (PRT, Padua Rehabilitation Tool; P&P, Paper & Pencil)*

NPI Distress

The results show a significant effect of group ($\chi^2(2)$=13.47, p<.01) and a significant effect of the interaction between time and group ($\chi^2(4)$=9.82, p=.04). Similar to the results observed for NPI FxS, post-hoc comparisons show a significant difference at t0 between PRT and no treatment ($t_{59.87}$=-4.052, p<.001) and P&P ($t_{59.87}$=3.597, p<.001) groups. These difference became no longer significant at t1 (PRT vs no treatment: $t_{59.87}$=-2.019, p=.07; PRT vs P&P: $t_{59.87}$=2.345, p=.06). Indeed, the PRT group was the only group that showed a significant improvement between t0 and t1 ($t_{65.25}$=2.840, p<.01) maintained at t2 ($t_{70.70}$=3.237, p<.01). **Figure 9** shows how no treatment and P&P groups maintained a stable performance overtime while PRT group significantly improved.
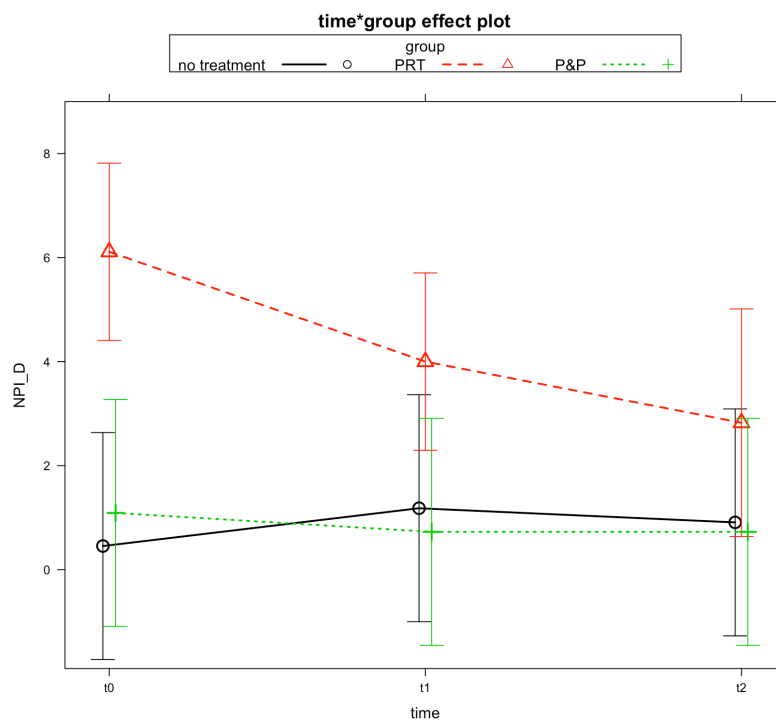
Figure 9 *Effect Plot with confidence bounds in NPI Distress. (PRT, Padua Rehabilitation Tool; P&P, Paper & Pencil)*

CSDD

The results show a significant effect of time ($\chi^2(2)$=9.62, $p<.01$). The post-hoc comparisons reveal a significant improvement at t1 in the PRT group ($t_{69.74}$=2.518, $p=.04$), maintained at t2 ($t_{75.66}$=2.223, $p=.04$) and a significant improvement in the P&P group between t0 and t2 ($t_{69.74}$=2.684, $p=.02$). Indeed, **Figure 10** shows how no treatment group maintained a stable performance overtime while PRT and P&P groups significantly improved.
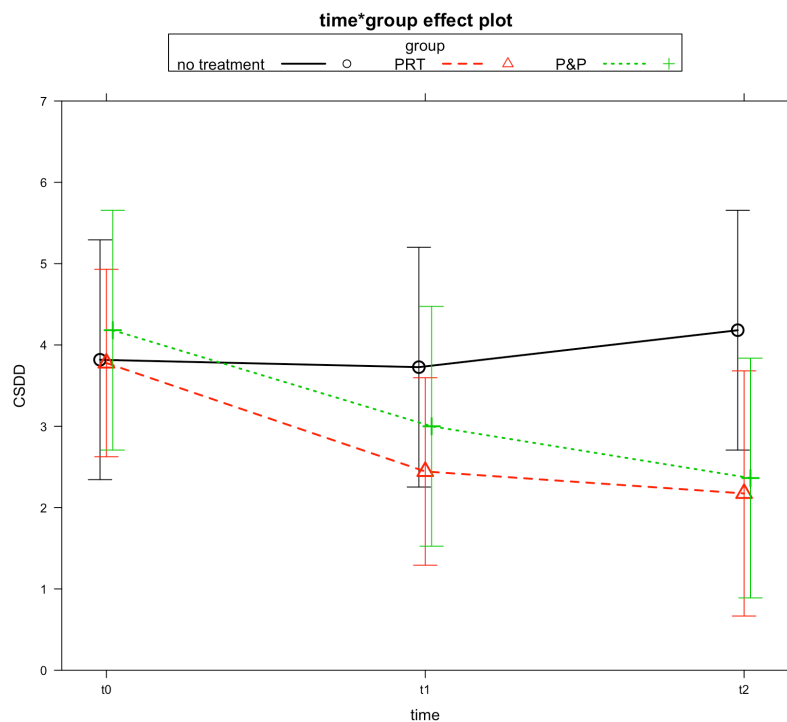
Figure 10 *Effect Plot with confidence bounds in CSDD. (PRT, Padua Rehabilitation Tool; P&P, Paper & Pencil)*

Discussion

The effects of cognitive training in patients with dementia have been widely discussed in literature. The results are controversial and while some reviews conclude that it leads to no positive or adverse effects (e.g, Bahar-Fuchs et al., 2013), others reviews using less restrictive criteria state that cognitive training is promising in the treatment of AD, with primarily medium effect sizes for learning, memory, executive functions, activities of daily living, general cognitive problems, depression, and self-rated general functioning (e.g., Sitzer et al., 2006). Studies - also with Italian population - showed improved cognitive performances after a cognitive training compared to waiting-list controls or to attention-placebo controls (Bergamaschi et al., 2013; Cahn-Weiner et al., 2003; Loewenstein et al., 2004; Mapelli et al., 2013; Requena et al., 2006). Moreover, the constantly developing of new technologies is giving new opportunities to researchers and clinicians in implementing new cognitive interventions. For example, the touch-screen technology in the development of software for cognition is widely used in patient with acquired brain injury as described by studies that used *Lumosity* (Toril et al., 2016; Wentink et al., 2016; Zickefoose et al., 2013), *Constant Therapy* (Des Roches et al., 2014; Kiran et al., 2014; Mark et al., 2016), and *CogniFit* (Gigler et al., 2013; Haimov & Shatil, 2013; Peretz et al., 2011). The touch-screen technology proved to be easy to use and allows to develop entertaining cognitive training. Yet, no touch-screen software are available for Italian population and in particular for patients with dementia. Thus, we decided to develop a tool using touch-screen technology for cognitive training: The Padua Rehabilitation Tool. In this study we aim to test the efficacy and examine the effects of this software in a population of Italian patients with dementia recruited in multiple care centers. We recruited 40 patients and randomly assigned to three groups: (1) a no treatment group involved in activities normally programmed by the care center (watching Tv, playing cards, singing …), (2) the Padua Rehabilitation Tool (PRT) group, involved 4 times a week for 5 weeks (20 session) in a cognitive training using the software developed by us, and (3) a traditional group (P&P) involved in classic paper & pencil exercises for the same amount of time. Considering that the Padua Rehabilitation Tool is based on the paper and pencil exercises used in P&P group we hypothesize to find comparable results between two groups. Indeed, we are comparing two similar cognitive training different for the delivering modality (paper and pencil Vs touch-screen) against a no treatment. Thus we hypothesize that the use of touch screen does not lead to higher cognitive improvement if compared to paper and pencil rehabilitation but at least at same results: the advantages of using this technology rely on usability, portability, precision and motivation aspects rather than in efficacy. The patients can use the software outside clinic, and they can receive a tailored rehabilitation, controlled by remote by the clinician. Results support this hypothesis. We examined the effects on both measures of cognitive functioning and measures of neuropsychiatric symptoms.

Regarding the cognitive measures, the analyses on MMSE scores showed how performance overtime of the groups is different. Particularly, the patients in the no treatment group maintained their performance stable or slightly decreasing. On the other side, patients that received a treatment significantly improved the cognitive performance overtime: while there were not significant differences between group at t0, at t1 and t2 no treatment group is significantly different compared to the others (see **Figure 6**). Moreover, the results on the ADAS revealed that, albeit the groups were not paired at t0, the PRT group was the only one with a significant improvement in cognitive functioning between t0 and t2. The same trend was observed in the P&P group although the effect was not significant (see **Figure 7**). Regarding the neuropsychiatric symptoms none of the patients recruited had clinically relevant symptoms. But, thanks to the measure used it was possible to quantify the frequency, severity and distress of such symptoms even if they are not clinically relevant. Results at NPI FxS (frequency multiplied severity) subscore showed that in case of presence of some symptoms, a cognitive intervention could be helpful in reducing such symptoms. Indeed, the PRT and the P&P groups had a slight presence of neuropsychiatric symptoms at t0 that were significantly reduced at t1. Moreover, the results were maintained at t2 (see **Figure 8**). Same pattern was observed for the distress associated to the symptoms in the PRT group (see **Figure 9**). Similar are the results at the CSDD: albeit there were no clinically relevant symptoms, patients in the PRT and P&P groups significantly improved their depressive symptomatology compared to the no treatment group (see **Figure 10**).

Firstly, the results of this study showed that a cognitive intervention with paper and pencil exercises is effective in patients with dementia in reducing the cognitive decline, improving the cognitive performance after treatment and reducing the neuropsychiatric symptomatology. These results support previous evidences (Bergamaschi et al., 2013; Mapelli et al., 2013; Spironelli et al., 2013). Secondly, it is showed that these results are maintained one month after the end of treatment. Thirdly, this study demonstrates that the Padua Rehabilitation Tool brings to results comparable to paper and pencil rehabilitation and thus, it is demonstrated his efficacy in patients with dementia. It is possible to conclude that the software could be used for cognitive training. This is an important implication because it provides a scientific base for a completely novel tool for rehabilitation in the Italian context. Undoubtedly, this study has several strong points. First of all, the choose of a complete assessment including measures of cognitive functioning and measures of neuropsychiatric symptomatology. Secondly, in order to test the efficacy of the PRT we decided to compare it not only with a no treatment group, but also with an active condition that previously proved to be effective. Indeed, the need for active control groups has been highlighted in general within the cognitive training literature (Green, Strobach, & Schubert, 2013; Klingberg, 2010), and more specifically in investigations of

healthy adults (Boot et al., 2013), older adults (Smith et al., 2009; Valenzuela & Sachdev, 2009) and in multiple sclerosis (Morrison & Chein, 2011). Moreover, the use of analyses that consider different baseline for each subject accounting for heterogeneity is of fundamental importance when we deal with patients and in particular in dementia where is largely documented that the cognitive profiles could be very different (Cohen-Mansfield, 2000; Kehagia et al., 2010; Ritchie & Touchon, 1992; Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011; Wallin & Blennow, 1993).

Limits and Future studies

While this study has several strong points it is not exempt of some limitations. Firstly, the groups are paired only for age, education, and MMSE scores. Thus, it is possible to encounter cases where the groups are significantly different already at t0 (e.g., ADAS) making more complicated the generalization of results. However, considering the high correlation between ADAS-Cog and MMSE reported in literature (Weyer, Erzigkeit, Kanowski, Ihl, & Hadler, 1997) and confirmed in this study (r=-.73, $p<.001$), remain unclear why the groups are different at t0. Secondly, while it was considered a follow-up one month after the end of treatment, it could not be enough to investigate the maintenance of improvements for longer times. Future studies may will include further assessment faraway the end of treatment (e.g., 3 months, 6 months or longer) as previous studies did (Ball et al., 2002; Cahn-Weiner et al., 2003; Loewenstein et al., 2004; Quayhagen & Quayhagen, 1989; Quayhagen, Quayhagen, Corbeil, Roth, & Rodgers, 1995). Moreover, this study is not under double-blind condition. Authors pointed out that it is hard to see how double-blind conditions can be applied in rehabilitation because therapists and psychologists cannot be blind to the treatment they are giving and in most cases neither can patients be blind to the treatment they are receiving (Mai, 1992; Wilson, Gracey, & Evans, 2009). However, it is possible to conduct single-blind trials where the assessor does not know which treatment has been provided. In this study was not possible to adopt either this condition but definitely future studies should overcome this limit. Future studies could also compare different volumes of training with PRT: given the variability observed in previous studies, it is not yet possible to determine the minimum required frequency, volume or duration of cognitive training and explicit dose-response trials in MCI are needed. High volume cognitive exercise appeared to result in greater benefit than lower volumes of training. Very frequent training for twelve weeks led to greater effect on memory (Rozzini et al., 2007) than longer, less regular training (Günther et al., 2003; Olazarán et al., 2004), and cognitive exercise studies generally had a higher frequency of training sessions at four (Cipriani, Bianchetti, & Trabucchi, 2006; Talassi et al., 2007) or five sessions per week (Barnes et al., 2009; Rozzini et al., 2007). In our study we programmed high frequency training sessions (four per week) for a short term training (5 weeks). It could be interesting to compare the results with a different duration of training.

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Chapter_6 Use of PRT in patients with acquired brain injury: singles cases and a pilot study

In the previous chapter I described the efficacy of an innovative cognitive training, using touch-screen technology, in patients with dementia. The attempt to delay the onset of age-related brain changes in the ageing brain and in degenerative conditions such as dementia and Parkinson's disease is one of the areas of intervention with computerized cognitive training (Bahar-Fuchs et al., 2013; Calleo et al., 2012; Gates & Sachdev, 2014; Lampit, Hallock, & Valenzuela, 2014; Walton, Mowszowski, Lewis, & Naismith, 2014). Other areas in which use of computerized cognitive training has been investigated are the improvement and treatment of cognitive disorders and acquired cognitive impairments in the developing child brain (Melby-Lervåg & Hulme, 2013; Shinaver, Entwistle, & Söderqvist, 2014), and the treatment of cognitive functioning in neuropsychiatric conditions (Anaya et al., 2012; Medalia & Choi, 2009). Lastly, the use of computerized cognitive training has been evaluated for treatment of the cognitive functions in adult acquired brain injury (ABI) providing encouraging evidences supporting the efficacy of these trainings (Bogdanova et al., 2015; Sigmundsdottir et al., 2016). Considering the previous positive results obtained using the Padua Rehabilitation Tool in patients with dementia and aware of the efficacy of computerized training in population with acquired brain injury we decided to test the effects of our tool in rehabilitation of these patients. Thanks to the flexibility of this software it was possible to define cognitive rehabilitation programs specific tailored to the needs of single patients with acquired brain injury. Thus, in this chapter, I report other experiences with the Padua Rehabilitation Tool. In order to protect and hide the real identity of patients, pseudonyms are used.

Anna: an early post coma cognitive rehabilitation

Anna is a women of 56 years old, married and with a twenty-years old son. She has a junior high school degree and she works as a nurse. Anna is 1.48m tall and weighs 165kg (BMI: 75.3) when she needed the care of a bariatric surgeon. Three months after a bariatric surgery, she had an unexpected and rapid worsening of medical condition because of a severe sepsis resulted in coma. The state of coma lasted about 35 days, during which she received a sensory stimulation program composed of auditory and tactile stimulation (Oh & Seo, 2003; Sosnowski & Ustik, 1994). Auditory stimulation was administered by music, the voice of family members and of clinicians. For tactile stimulation, touch of stimuli with different textures was applied. Two months after the awakening Anna started a cognitive rehabilitation program using the Padua Rehabilitation Tool. In total, Anna completed 37 sessions in around 5 months. The sessions were administered in intensive care unit were she was

hospitalized for most of the time. This is the first relevant aspect because some characteristics of the clinical settings may have had an influence on Anna's psychophysical status and on the sessions' realization. More in the specific appeared to be relevant: (1) modifications in circadian rhythm, because of external cues in the local environment such as 24-hour enlightenment and uninterrupted sound of medical apparatus; (2) frequently suspensions of the sessions because of other medical staff (physical therapist, dietician …); (3) frequently modifications of mood because of drug prescription or related to the physical malaise. Since the beginning Anna showed a positive and collaborative attitude, despite the important limitations related to the medical condition: she was bedridden and mechanically ventilated through a tracheostomy tube. Thus, Anna had a reduced motility and she was unable to communicate. She remained with mechanical ventilation for one month; after that it was possible to communicate directly with language and her motivation rapidly increased.

Considering the starting conditions was not possible to assess Anna with paper and pencil standardized tests. Thus, the baseline assessment consisted of clinical observation reporting:

- Low levels of orientation in time and space;
- Moderate comprehension, responding correctly to simple instructions;
- Moderate focused attention on stimuli presented;
- Low level of sustained attention

The cognitive rehabilitation with PRT at the beginning was focused on exercises for the stimulation of basic cognitive functions (identification, orientation and attention) and then to more complex abilities such as memory, language, and motor control. The cognitive rehabilitation ended almost 5 months later when Anna was dismissed from hospital. At the end of treatment, it is possible to report some important improvement both quantitative, related to performance at the PRT', and qualitative. She was also assessed with Mini Mental State Examination (MMSE) (Folstein et al., 1975) and with Esame Neuropsicologico Breve 2 (ENB 2) (Mondini et al., 2011), a neuropsychological battery that includes 14 subtests: digit span, immediate and delayed recall prose memory, Brown Peterson technique, Trail Making Test parts A and B, token test (5 items), word phonemic fluency, abstraction, cognitive estimation test, intricate figures test, house figure copy, daisy drawing test, clock drawing test, and ideomotor apraxia test.

Examining the performance of Anna in the specific exercises of PRT divided by cognitive domain, it is possible to report:

- improvement in orientation domain with less errors and faster response time (see **Figure 11 a**)
- improvement in memory domain with increased levels of difficulty, less errors and faster response time (see **Figure 11 b**)
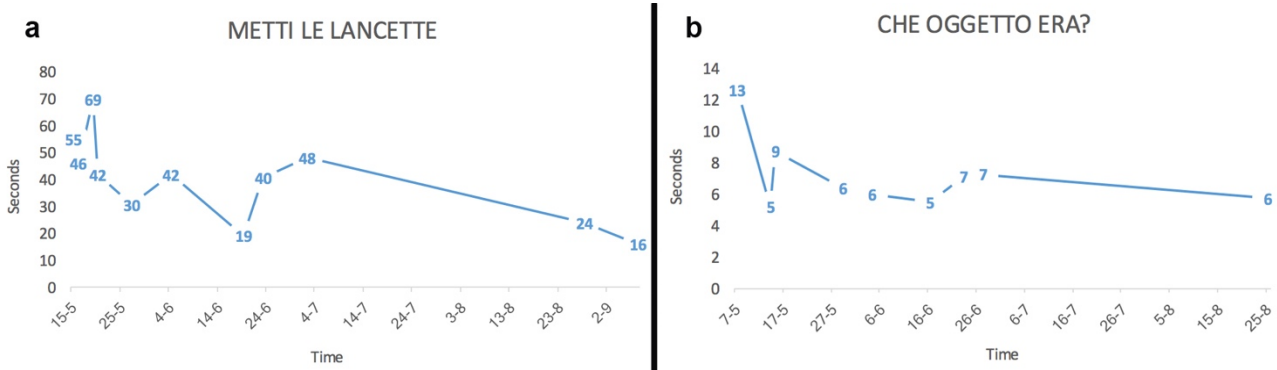
Figure 11 *Response Time (seconds) over time. a: "Metti le lancette"; b: "Che oggetto era?"*

- reduction of reaction time and errors in the attention domain. In particular Anna starting from exercises that require only selective attention is gradually arrived to complete exercises that require sustained and divided attention (e.g., from TMT A to TMT B);

- slight increase in levels of difficulty and improvement in response time in motor control domain (see **Figure 12**)
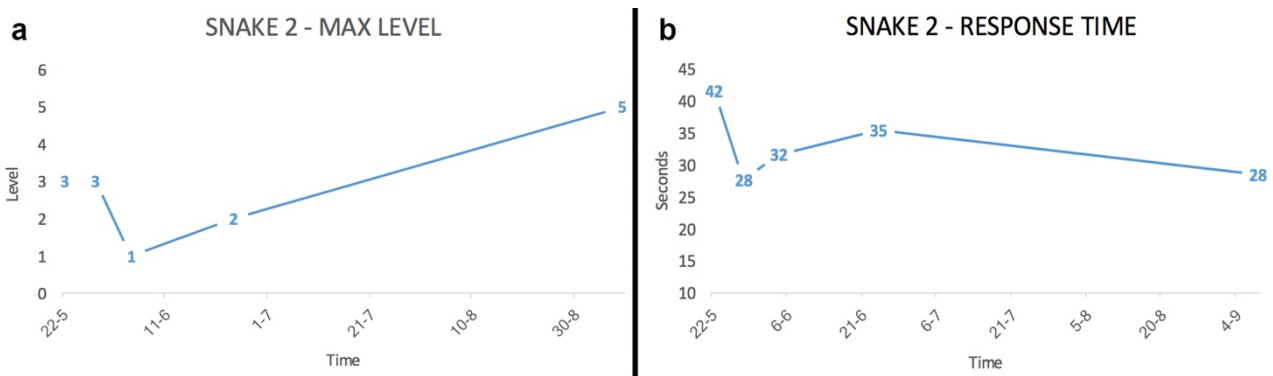
Figure 12 *Max level for session (a) and response time (b) for "Snake 2" exercise*

- relevant improvement of difficulty level in language domain related with stable response time and errors (see **Figure 13**)
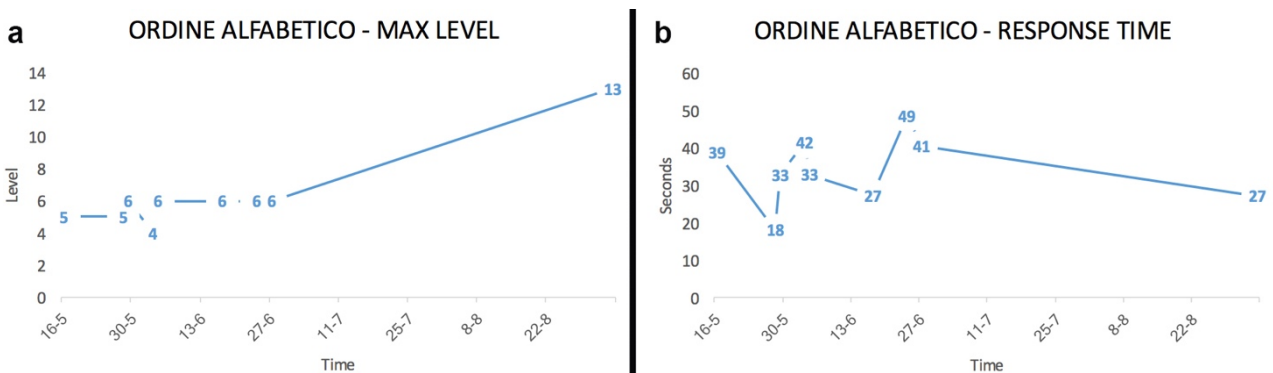
Figure 13 *Max level for session (a) and response time (b) for "Ordine alfabetico" exercise*

From the analyses of the performance at the PRT emerged important fluctuations: the widest could be explained by temporary confusional state caused by the adverse effects of changing medication.

At the end of treatment Anna was also assessed with standardized tests: she had the maximum score at MMSE (30) and a normal total score at ENB 2. **Table 7** shows the score and the outcome compared to a normal sample (matched for age, sex and education), at each test of ENB 2.

Table 7 Raw score and outcome at each subtest and total score of ENB 2

SubTest	*Raw score*	*Outcome*
Digit Span	5/8	Within normal range
Immediate recall prose memory	18/28	Within normal range
Delayed recall prose memory	20/28	Within normal range
Brown Peterson technique – 10 sec	6/9	Within normal range
Brown Peterson technique – 30 sec	5/9	Within normal range
Trail Making Test - A	45 sec	Within normal range
Trail Making Test - B	152 sec	Within normal range
Token Test	5/5	Within normal range
Word phonemic fluency	7,3	Below normal range
Abstraction	3/6	Lower limit of normal range
Cognitive estimation	5/5	Within normal range
Intricate figure test	28	Within normal range
House figure copy	1/2	Below normal range
Daisy drawing test	2/2	Within normal range
Clock drawing test	9,5/10	Within normal range
Apraxia test	6/6	Within normal range
Total Score	**68,15**	Within normal range

Furthermore, some qualitative aspects can help to understand the improvement in the cognitive functioning of Anna. For example, at the beginning of treatment she had a severe damage on sustained attention: she was unable to maintain the attention on stimuli and the session with PRT lasted no more than 10 minutes. At the end of treatment, however she was able to use the software continuously for minimum 1h without problem. Moreover, Anna definitely improved in the autonomy in the use of the software: at the beginning of treatment, the obvious motor problems impeded the use of software and she needed help for pointing the stimuli and giving the answer, while at the end of treatment she was completely able to manage the software and the touch-screen in complete autonomy. Furthermore, experiencing the first successes and acquiring more awareness of her own limits Anna' motivation rapidly increased and at every session she tried to improve herself.

In conclusion, Anna started a cognitive rehabilitation following a coma state (~30 days) caused by a severe sepsis. At the beginning of rehabilitation, she was cognitively unable to complete a neuropsychological assessment because of her severe attention deficits and orientation in space and time. She was hospitalized in an intensive care unit and thus she was bedridden and with a tracheostomy tube. After 5 months of rehabilitation Anna was dismissed from the hospital: her performance in neuropsychological tests was completely normal and the performance at PRT revealed a relevant improvement generalized to the different cognitive domains. The duration of the

session increased from maximum 10 minutes to minimum 1h, she was able to manage the software alone and she definitely increased her own awareness and involvement in the rehabilitation process. Lastly, it is important to highlight one big advantage of use a portable tool for deliver rehabilitation: thanks to the use of a tablet it was possible to reach the patients in the early stage after coma in the context of an intensive care unit were usually is impossible to deliver other type of cognitive rehabilitation.

A Pilot study in stroke patients

Here I present the results of a pilot study for testing the effects of a cognitive rehabilitation with PRT in patients with stroke. Four patients (Mean Age: 71.3; SD: 7.4; 2 males) were recruited at the Modulo di Neuropsicologia Riabilitativa, Ospedale San Giorgio (Ferrara). They were evaluated for their eligibility by the neurologist and neuropsychologist of the care center. The inclusion criteria consisted in a score greater than 6 at the Level of Cognitive Functioning Scale (LCF) (Hagen, Malkmus, & Durham, 1972), the absence of evident behavioral and neuropsychiatric symptoms. Also, patients were able to communicate and understand verbal and written language and physically able to interact with the software using one upper limb - not necessarily the dominant limb. The patients used the Padua Rehabilitation Tool five times a week for one month (20 sessions). Each session lasted for about 1h. The exercises to be conducted with each patient have been chosen on the base of their cognitive profile as result of the neuropsychological assessment. Patients were assessed with Esame Neuropsicologico Breve 2 (ENB 2) (Mondini et al., 2011) before and at the end of treatment. It is the same software of ENB 2 that, comparing test and retest scores, provides the significance of change in cognitive functioning showing whether performance in the different sub-tests remains stable, improves or decreases.

Table 8 shows the comparison between test and retest for each patient: in green are highlighted the significant improvements; in red are highlighted the significant impairments; the other cells represent a stable performance overtime. Clearly, patients n.1, n.3 and n.4 showed a significant improvement in the cognitive functioning. For example, patient n.1, a 71-years old woman with anomia and a right-sided hemiparesis caused by an ischemic stroke. Despite the hemiparesis on the dominant limb, she was able to use the software with the non-dominant arm. Results at the end of treatment showed a significant improvement in the subtest focused on the language domain: she had a significant and clinical improvement in the word phonemic fluency test and in the token test. Moreover, she showed a generalized improvement to measures of memory and working memory such as the immediate and delayed recall prose memory test and the Brown Peterson test (30 sec).

Table 8 *Test-retest scores at each subtest of ENB 2 for each patient*

Subtest	Patient 1			Patient 2			Patient 3			Patient 4		
	t0	t1	Effect	t0	t1	Effect	t0	t1	Effect	t0	t1	Effect
Digit Span	5	5	=	4	5	+	5	6	+	6	6	=
Immediate recall prose memory	4	13	+	11	10	=	16	15	=	3	6	+
Delayed recall prose memory	1	12	+	19	14	-	13	18	+	5	7	+
Brown Peterson technique – 10 sec	3	2	=	2	3	=	3	6	+	6	8	=
Brown Peterson technique – 30 sec	0	4	+	4	5	=	5	3	=	9	8	=
Trail Making Test - A	80	90	=	164	182	-	160	90	+	130	35	+
Trail Making Test - B	N.E*	N.E	=	999	580	+	999	185	+	N.E	195	+
Token Test	3.5	5	+	5	5	=	5	5	=	4	5	=
Word phonemic fluency	2.3	8	+	3	6	+	3	7	+	2	7	+
Abstraction	5	6	=	6	6	=	6	6	=	2	6	+
Cognitive estimation	3	4	=	5	5	=	5	5	=	5	5	=
Intricate figure test	12	18	+	17	12	-	12	20	=	4	25	+
House figure copy	2	1	=	0	0	=	2	1	-	1	1	=
Daisy drawing test	2	2	=	2	2	=	1	1	=	2	2	=
Clock drawing test	7.5	8.5	=	5	4	=	8.5	8.5	=	7	9.5	+
Apraxia test	4	5	+	6	6	=	5	5	=	6	6	=

Note: The red scores are less than the cut-off, adjusted for age and education of each patient. The Black scores are within normal range. In the column "Effect" the significant changes overtime, computed by the software included in the ENB 2, are reported (= stable performance; + improvement; - impairment).
* N.E, Non-executed

Patient n.3, a 70-years old man, showed cognitive deficits result of a dx fronto-temporal ischemic stroke. Particularly below the normal range were the scores in tests of visuo-spatial attention, divided attention, and in word fluency. At the end of treatment, there were significant improvements in all these tests: he was faster in the completion of TMT A (160 sec at t0 Vs 90 sec at t1), he completed the TMT B within normal range of score (185 sec), and he had a significant improvement in the word phonemic fluency test. Moreover, he showed a generalized improvement in measures of memory such as the digit span, the Brown Peterson test (10 sec) and the delayed recall prose memory test. In this last test is particular relevant how it is improved the patient' ability in organizing the memory for a better recalling.

Patient n.4 was a 81-years old man with outcomes of a hemorrhagic stroke in dx fronto-parietal and mesial temporal lobe. He showed deficit in short-term memory, in lexical access, and in the ability to segregate stimuli from the background with scores below the normal range in the recall prose memory tests, in the word phonemic fluency test and in the intricate figure test. In this last test he was really slow and he gave up before the end of available time. At the end of treatment, first of all he significantly improved in all these tests moving from "below the normal range" to "within the normal

range" scores. In particular, in the Intricate figure test he recognized 21 figures while at t0 he recognized only 4 figures and in the Word phonemic fluency test he recalled 7 words against the only 2 words at t0. Moreover, he improved in other test. Similar to patient n.3, he was faster in the completion of TMT A (130 sec at t0 Vs 35 sec at t1), and he completed the TMT B within normal range of score (195 sec). Finally, he accurately planned the clock draw, carefully positioning the numbers respecting the horizontal (12-6) and vertical axis (9-3) realizing a precise representation.

On the other hand, results of patient n.2 are controversial. She is a 63-years old woman on a second episode of ischemic stroke. At t0 she presents evident deficits of visuo-spatial, selective and divided attention. Moreover, she presented a slight working memory deficit and a deficit in mental representation, and planning abilities. At the end of treatment, she achieved some significant improvement but also some significant impairment. In particular, she improved in measure of short-term memory (Digit span), divided attention (TMT B) and in lexical retrieval (Word phonemic fluency). Also, she showed a significant worsening in the Delayed recall prose memory test, in TMT A and in the Intricate figure test. These results could be explained by an important qualitative consideration. Indeed, trying to be more accurate the patient was slower in the completion of the tests. For example, at TMT A, before drawing the line, she joined the numbers mentally making sure of not omitting some stimuli. Surely, this strategy resulted in slower completion time and thus in a worse score. The same observation could be extended to the Intricate Figure test: trying to avoid errors of denomination she was slower in naming the stimuli and thus she reported less figures.

Furthermore, to all patients at the end of treatment was administered an ad-hoc questionnaire to assess the user experience with the Padua Rehabilitation Tool. This questionnaire included six questions in 6-point Likert scale. The questions investigated: (1) attractiveness; (2) clarity; (3) usability of touch-screen; (4) pleasantness of exercises; (5) learnability; (6) motivation. The results showed high scores of Padua Rehabilitation Tool for each one of these dimensions (**Figure 14**).
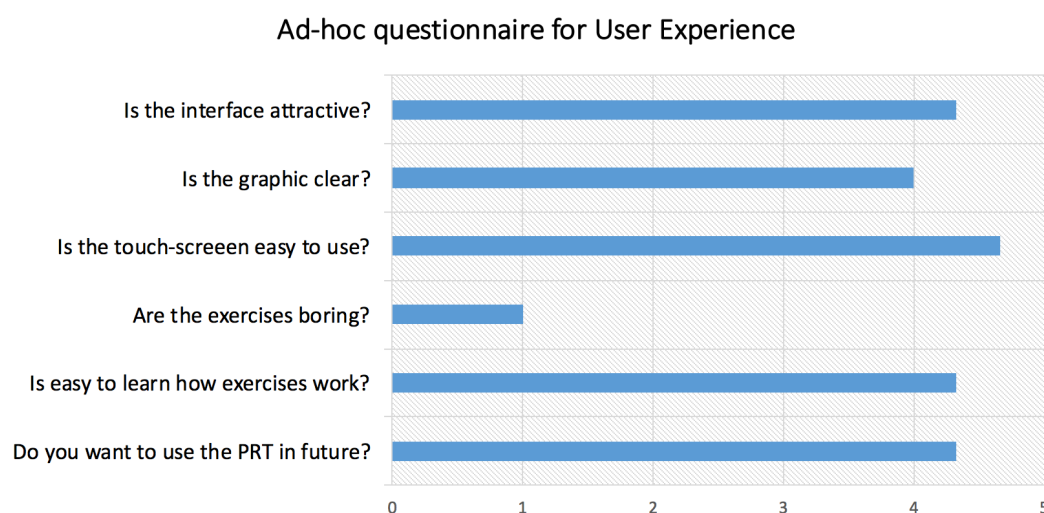
Figure 14 Mean scores at the ad-hoc questionnaire for user experience

Summarizing, these preliminary results suggest that Padua Rehabilitation Tool can be used as tool for cognitive rehabilitation in patients after stroke. All patients involved in this study showed significant improvement in the standardized tests related to their main deficit. Also there were reported some generalization effects in other cognitive domains. For example, patient n.1 received a treatment focused on anomia and in general on language: other than improvement in language tests she showed significant improvement in memory tests. Lastly, this pilot study highlights a big advantage in using touch-screen technology with stroke patients: 81% of the stroke patients are initially hemiparetic (Barker & Mullooly, 1997; Sommerfeld, Eek, Svensson, Holmqvist, & Von Arbin, 2004) and 60% of the post-stroke individuals continue with residual motor dysfunction as a long-term disability after the first year (Cauraugh, Light, Kim, Thigpen, & Behrman, 2000). Thus, became of primary importance the use of technologies that allow patients with motor impairment an easy interaction: using the non-dominant hand, it is definitely easier the interaction with a touch-screen, differently from the use of a mouse or a keyboard. This is confirmed in this study, where two patients with hemiparesis of the dominant limb used the software with the non-dominant hand without a specific learning.

Andrea and Mario: two cases of cognitive rehabilitation following Traumatic Brain Injury

This paragraph includes the brief description of two patients recruited at Gruppo Veneto Diagnostica e Riabilitazione, Cadoneghe (Padova). Both followed a cognitive intervention with Padua Rehabilitation Tool three times a week for seven weeks (20 sessions). They were assessed before and after treatment with Esame Neuropsicologico Breve 2 (ENB 2) (Mondini et al., 2011).

Andrea, a 42-year old IT technician, lives with his partner and has no kids. Eight months before the beginning of treatment with Padua Rehabilitation Tool because of a fall he received a brain injury and a severe facial trauma. The consequences of this trauma were a right-sided hemiparesis and a non-fluent aphasia. He showed deficits in lexical retrieval and in phonetic/phonological processing, and an apraxia of speech. Moreover, he showed some deficits in executive control, such as impulsivity, irritability and low ability to regulate behavior. Andrea assessment at t0 showed a severe impairment in all the sub-test except the Daisy drawing test. Albeit the same picture was observed at t1, there were some improvements (see **Table 9**): a slight improvement in Digit Span going from 0 to 3 digits retained (cut-off: 5); he completed the TMT B in 230 seconds while at t0 he was not able to perform the task (cut-off: 142); and he improved in the Clock drawing test going from 0 to 3 (cut-off: 8).
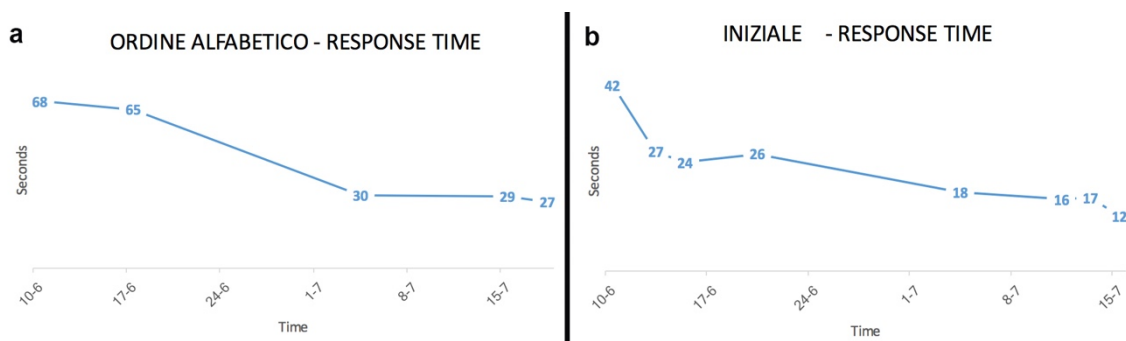
Figure 15 Andrea. Mean response time at (a) "Ordine Alfabetico" and (b) "Iniziale" exercises

Although the cognitive functioning captured with the standardized tests remained severe, there are some important qualitative considerations indicating a slight improvement. First of all, Andrea improved his fine motility. Despite the right-side hemiparesis he was instructed to use the hemiparetic arm for completing the exercises: he definitely improved his fine motility overtime, acquiring more awareness of the position of the hand in the space and controlling the fingers for pointing and dragging stimuli on the screen.

Secondly, he showed some relevant improvements in language production. While at the beginning of treatment his production was typified by phonological paraphasias, during treatment he started to produce some semantic paraphasias. For example, naming the figure of an "ambulance", while at the beginning of treatment Andrea was able to pronounce only some phoneme, continuing treatment he started to say "croce verde" producing semantic paraphasias.

Lastly, Andrea slightly improved in the metacognitive awareness of his own deficits and this might have favored the compliance with the treatment. From the analyses of the performance at Padua Rehabilitation Tool emerged that Andrea improved in particular in the response time (e.g., "ordine alfabetico", "iniziale") and in the number of errors (see **Figure 15** and **Figure 16**).
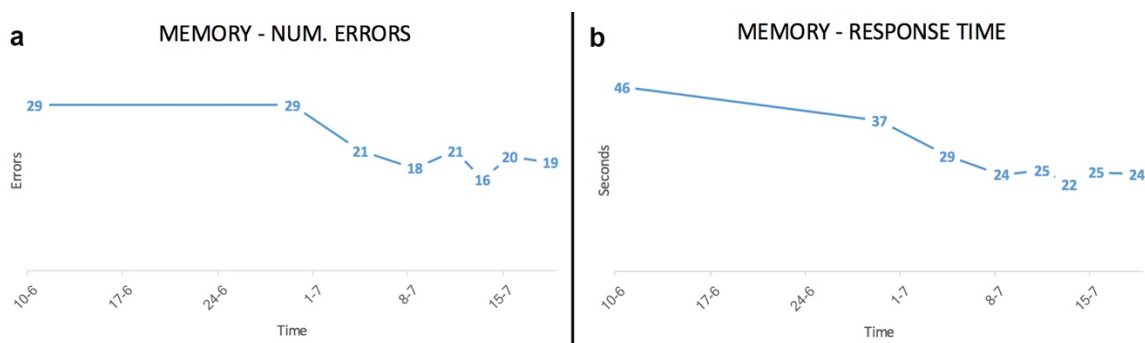
Figure 16 Andrea. (a) Number of errors and (b) mean response time at "Memory" exercise

Mario, a 47-year old workman, is divorced with 2 sons. He has 8-year of education and currently lives with his parents. 3 years before the beginning of the cognitive intervention with Padua Rehabilitation Tool, he had a car accident resulted in a brain injury that caused anomia. He also showed deficits in short-term and long-term memory, in selective and in divided attention. The results

at the neuropsychological assessment at the end of treatment revealed some significant improvements. Comparing the neuropsychological assessment before and after treatment, Mario improved in test of short-term memory (Digit Span) and in test of long-term memory (Delayed recall prose memory); he also improved in a measure of selective and visuo-spatial attention (TMT A) and in lexical retrieval (Word phonemic fluency). Regarding the tests for apraxia and abilities of mental representation results are controversy: Mario improved in the house figure copy but he definitely made worse in the daisy drawing test and in the clock drawing test (see **Table 9**).

The analyses of performance at Padua Rehabilitation Tool revealed faster response time in most of the exercises (e.g., "Iniziale", "Sequenza Temporale", "Sillabe", "Snake") (see **Figure 17**)

Table 9 *Test-retest scores at each subtest of ENB 2 for Andrea and Mario*

Subtest	Andrea			Mario		
	t0	t1	Effect	t0	t1	Effect
Digit Span	0	3	+	3	6	+
Immediate recall prose memory	6	2	-	6	9	+
Delayed recall prose memory	1	0	=	6	14	+
Brown Peterson technique – 10 sec	0	0	=	4	4	=
Brown Peterson technique – 30 sec	0	0	=	5	4	=
Trail Making Test - A	84	72	=	145	55	+
Trail Making Test - B	N.E.*	230	+	135	178	=
Token Test	1.5	1	=	4.5	4.5	=
Word phonemic fluency	0	0	=	4.3	8.33	+
Abstraction	0	0	=	2	3	+
Cognitive estimation	1	0	=	3	4	+
Intricate figure test	13	15	=	13	16	=
House figure copy	1	1	=	1	2	+
Daisy drawing test	2	1	-	2	0	-
Clock drawing test	0	3	+	10	5.5	-
Apraxia test	3	4	=	4	6	+

Note: The red scores are less than the cut-off, adjusted for age and education of each patient. The Black scores are within normal range. In the column "Effect" the significant changes overtime, computed by the software included in the ENB 2, are reported (= stable performance; + improvement; - impairment).

 * N.E, Non-executed
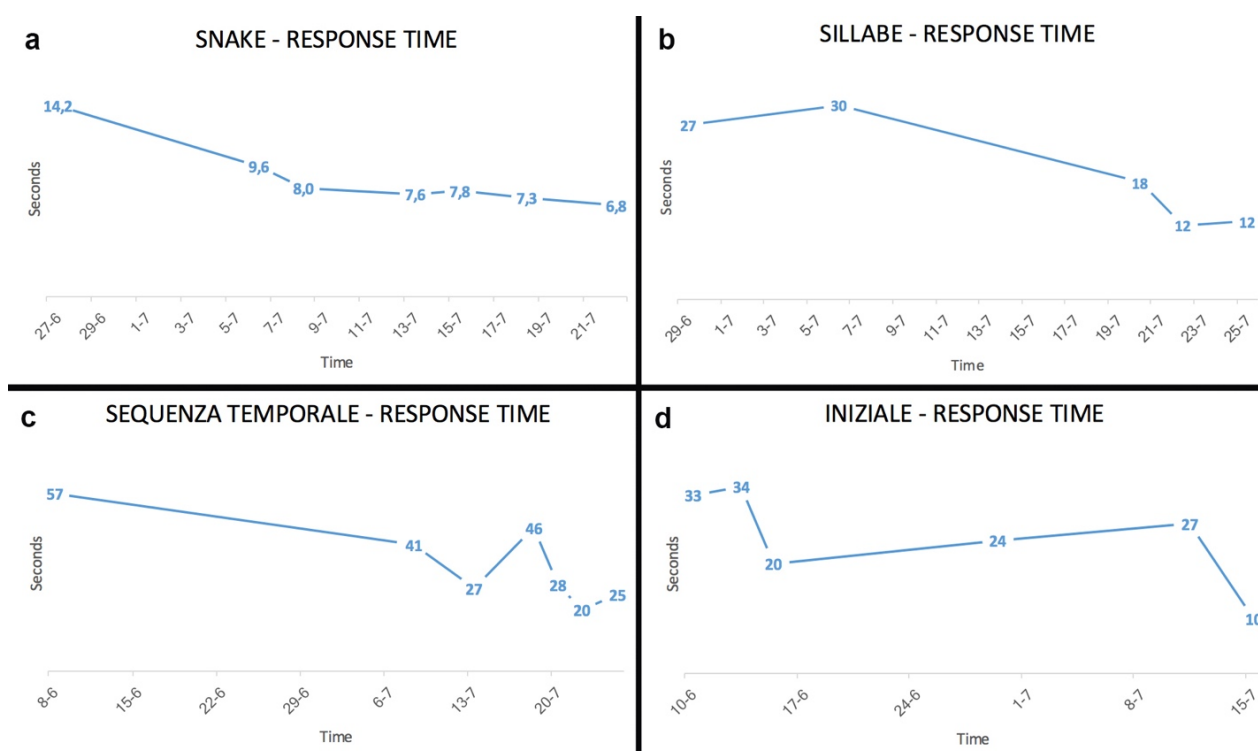
Figure 17 *Mario. Mean response time at (a) "Snake", (b) "Sillabe", (c) "Sequenza temporale", and (d) "Iniziale" exercises*

In conclusion, these two cases highlighted the possible effects of a training using the Padua Rehabilitation Tool in adult patients with cognitive deficits caused by traumatic brain injury. The two cases presented are very different each other. In the first one, Andrea, the quantitative changes (before-after treatment) are less evident compared to the second one, Mario. Andrea had severe cognitive deficits and he showed some qualitative improvements. On the other hand, Mario showed some important improvement in three different cognitive domains assessed by the standardized tests: attention, memory and lexical retrieval. Future studies are needed to better assess the effects of Padua Rehabilitation Tool on patients with traumatic brain injury.

Conclusions

The aim of this chapter was to present some experiences of using the Padua Rehabilitation Tool in patients with acquired brain injury. Surely these results cannot be intended as solid conclusion of the efficacy of the PRT in patients after stroke or traumatic brain injury. However, these results indicate that the Padua Rehabilitation Tool can be used in different context and that can be adapted and tailored to the different needs of patients. The results obtained are promising and it is demonstrated that patients can have significant improvement in neuropsychological assessment. The advantage of using a mobile touch-screen technology revealed to be of fundamental importance when it is needed to deliver a cognitive intervention in peculiar context, such an intensive care unit, or when the rehabilitation is addressed to patients with motor impairment and hemiparesis on the dominant side.

These results can be used as basis for future studies that surely are needed to test the efficacy of the Padua Rehabilitation Tool as tool for cognitive rehabilitation of patients with acquired brain injury.

CONCLUSIONS

The main aim of this dissertation was to describe the development and the application of an innovative tool for neuropsychological rehabilitation, the Padua Rehabilitation Tool. As like all the cognitive interventions, it lies on the assumption that brain has the ability to undergo functional and structural alterations in response to internal and external environmental changes. In Chapter 1, I described the multitude of different mechanisms that may underlies the causes of brain plasticity. For obvious reasons, I consider particularly relevant the literature related to the functional and structural connectivity changes as effect of a cognitive training. The first conclusion of different reviews is that cognitive rehabilitation is effective (Cicerone et al., 2000, 2005, 2011): there is sufficient information to support evidence-based clinical protocols, and to design and implement a comprehensive program of empirically-supported treatments for cognitive disability. Furthermore, are demonstrated training-induced changes in cerebral activation associated with cognitive interventions (Chen, Abrams, & D'Esposito, 2006; Couillet et al., 2010; Erickson et al., 2007; Kim et al., 2009; Takeuchi et al., 2010). Today, there are no doubts that brain plasticity is the basis for recovery from brain damage. It is a characteristic of our lifelong existence and thus brain reorganization is possible during our entire lifespan (Bach-y-Rita, 2003; Cicerone, 2012).

Once the basis for neuropsychological rehabilitation have been set, I focused the attention of this dissertation in what is establishing new frontiers in rehabilitation: the use technology (Chapter 2). It is clear how the field of neuropsychology is continuously shaped by the advancements in technology. The consequences of the digital revolution are evident both in neuropsychological assessment and in neuropsychological rehabilitation. A number of papers have described the promise of smartphone-based applications for cognitive assessment (Kwan & Lai, 2013; Lee et al., 2012; Thompson, Barrett, Patterson, & Craig, 2012). In one of these smartphone applications, Brouillette et al. (2013) developed a new application that utilizes touch-screen technology to assess attention and processing speed, finding evidences that support the potential of smartphone-based assessment batteries for attentional processing in geriatric cohorts. Moreover, the exponential increase in access to computers and the Internet allows for interactive Web-based cognitive assessments (Elbin, Schatz, & Covassin, 2011; Medalia, Lim, & Erlanger, 2005; Raz, Bar-Haim, Sadeh, & Dan, 2012; Scharre, Chang, Nagaraja, Yager-Schweller, & Murden, 2014; Troyer et al., 2014). On the other hand, there has been a recent proliferation of computer-assisted and other multimedia methods in neuropsychological rehabilitation, which reflects a general trend toward leveraging technology to improve the accuracy and efficiency of data capture procedures. This process led to "Neuropsychological Rehabilitation 2.0" (Parsons, 2016): the rehabilitation is moving beyond the limited technologies of the past to more

sophisticated technologies. For example, as Parsons says, "the memory notebooks used for training memory-impaired patients within a Neuropsychological Rehabilitation 1.0 framework would typically be small three-ring binders used for remembering appointments and other important information. In Neuropsychological Rehabilitation 2.0, these "memory notebooks" are handheld electronic devices such as smart phones, iPads, personal computers, and many other types of computerized devices." (Parsons, 2016, p. 116). Different reviews investigated and reported the effects of computerized training (Bayley et al., 2014; Bogdanova et al., 2015; Cha & Kim, 2013; J. B. Lee & Cherney, 2016; Sigmundsdottir et al., 2016; Zheng et al., 2016). The majority of studies reported improvements on tests of cognitive function. Some studies included outcomes reflecting generalization of computerized-cognitive training to measures that reflect a spectrum of self, informant and observer ratings of cognition in everyday life, ability during performance of activities, as well as whether or not there is participation in leisure, vocational, social, or educational activities. Lastly, very few studies incorporated neuroimaging studies to evaluate the neurological mechanisms of change. However, one particular technology that pushed the re-innovation of neuropsychological tools is the touch-screen technology. Since touch-screens literally put the fingers in touch with what is on the tablet screen, this technology is considered as the most natural of all input devices. Surely, this is a big step forward in the usability of a system. In particular, if compared to classic input devices such as keyboard or mouse or recent input such as the Nintendo Wii Remote that require much more hand-eye coordination. But the touch-screen technology alone is not enough for driving the innovation of "Neuropsychological Rehabilitation 2.0". Indeed, the first commercialized touch-screen computer was released in 1983, but is only when the touch-screen technology was implemented in portable devices that the real revolution took place. Since the release of the first-generation iPad (Apple Inc., Cupertino, USA) in 2010, we assist to the beginning of a new era of tablet devices and to an incredible diffusion of these devices among population. The direct consequence is the growing development of software for cognitive rehabilitation taking advantage of the portability of a device integrated with the most natural input technology. Thus, many software for cognition have been developed such as *Cogmed, Cognifit, Lumosity, BrainHQ, Rehacom, Neuronation, Memorado, Elevate, Constant Therapy*. Some of these were scientifically validated (e.g., Des Roches et al., 2014; Fernández et al., 2012; Gigler et al., 2013; Haimov & Shatil, 2013; Li et al., 2013; Smith et al., 2009; Thompson et al., 2016) some other were not. Anyway the aim of all the efficacies studies was to establish "if", and "how much" a specific computer program or a tablet software could be beneficial for patients. The Authors were interested in understanding if computerized training could improve cognitive functions such as working memory, attention, or language domains such as naming, reading or writing. The efficacy of the technology-based therapy

could be described as improvement in the specific exercises delivered by the program and on related exercises, or as improvement on standardized tests (ST). Importantly, there have not been attempts to align the exercises provided with computerized training with the ST. The previous studies were focused on reporting (1) only within task improvement (Crerar et al., 1996; Mortley et al., 2004; Ramsberger & Marie, 2007), (2) only improvement on impairment-based ST (Aftonomos et al., 1997; Cherney, 2010; Hoover & Carney, 2014; Linebarger et al., 2007), or (3) both within task improvement and ST improvement separately (Fridriksson et al., 2009; Kalinyak-Fliszar et al., 2015; Kurland et al., 2014; Raymer et al., 2006). To the best of my knowledge, none before investigated the relationship between this two different measures of outcome. This investigation is the aim of the study presented in Chapter 3. The perceived relationship is not necessarily automatically provided, thus, it is important to examine how exercises and ST are related, if improvement in therapy exercises mirrors improvement in ST. However, there are no studies that prove a predictive relationship that benchmarks gains in treatment with standardized outcome measures. Most of the time the attention is focused on demonstrating the degree of improvement on impairment-based measures from pre-treatment to post-treatment. While establishing the relationship between changes in therapy exercises and ST may seem unnecessary as it seem so obvious, it has an important implication: establishing such a relationship strengthens the validity and efficacy of the various impairment-related treatment that are utilized in cognitive rehabilitation. Finding a predictive relation between therapy exercises' performance overtime and standardized score could confirm that outcomes of treatment are directly connected to the treatment each patient received and specifically to the unique response of each patient to that. It would confirm that changes in performance on therapy exercises and in standardized test are not just in co-occurrence but are directly related each other and this relation allows the clinician to make predictions. In the study presented in Chapter 3, firstly, I described how is possible to match the different computer-based exercises with the different ST subscore. The result of this process is a view on the possible relationships between therapy exercises and ST. Then, I statistically investigated the strength of these relationships. Results demonstrate that exists a predictive relationship: there is a significant effect of post-treatment normalized score on computer-based exercises, controlled for the pre-treatment score, in the prediction of the standardized tests.

Once I demonstrated that a predictive relationship between the two dimensions of outcome exists, hence reinforcing the possible assumptions on effects of computerized training, in Section 2 of this dissertation I described the development (Chapter 4) and the use (Chapter 5 and 6) of the Padua Rehabilitation Tool. Until few years ago most of the computerized training software and in particular the software for tablet devices were unavailable in Italian language. Thus, the most innovative aspect of this dissertation is the development of a software for cognitive rehabilitation. In Chapter 4, I

discussed how I developed this software and which are his most important features focusing mostly on aspects such as the theoretical background, the flexibility, the usability and feedbacks rather than the programming part that I entirely coded by myself. Aware that a software should be written by a professional programmer, but considering that "ideally a programmer should work with a therapist who would guide the theoretical and clinical application aspects of the software." (McBain & Renton, 1997), I decided to develop the software by myself. Indeed, the recent tools for programming allow inexperienced programmers to develop basic software.

Originally, the Padua Rehabilitation Tool was designed for people with dementia and thus the most important study of efficacy was conducted on this population (Chapter 5). For the study, 40 patients with dementia were recruited in multiple care center and randomly assigned to three groups: (1) a no treatment group involved in activities normally programmed by the care center (watching Tv, playing cards, singing …), (2) the Padua Rehabilitation Tool (PRT) group, involved 4 times a week for 5 weeks (20 session) in a cognitive training using the software developed, and (3) a traditional group (P&P) involved in classic paper & pencil exercises for the same amount of time. They were assessed before the beginning of training, at the end, and one month after the end of treatment with both measure of cognitive functioning and of neuropsychiatric symptomatology. As described in Chapter 4, the Padua Rehabilitation Tool is inspired by the paper and pencil exercises included in Bergamaschi et al. (2008) and used in the P&P group. Therefore, I hypothesize to find a significant difference with no treatment group, but comparable results between PRT and P&P groups. I hypothesize that the use of touch screen does not necessarily lead to higher cognitive improvement if compared to paper and pencil rehabilitation but at least at same results: the advantages of using this technology rely on usability, portability, precision and motivation aspects rather than in efficacy. Results support this hypothesis. PRT and P&P groups had the same trend in all the measures of cognitive functioning and in the measures of neuropsychiatric symptoms. In many cases this trend was significantly different and in the opposite direction of the trend showed by the no-treatment group (e.g., MMSE, NPI Frequency x Severity). Firstly, the results of this study support the evidences of the efficacy of cognitive training in people with dementia (e.g., Cahn-Weiner et al., 2003; Koltai et al., 2001; Loewenstein et al., 2004; Mapelli et al., 2013; Requena et al., 2006). Than it is demonstrated that a cognitive training using the Padua Rehabilitation Tool, is effective such as a more classic paper and pencil approach to rehabilitation. Thus, the advantages in usability and portability of this tool are the first pragmatic reason to prefer a tablet device for deliver rehabilitation. Moreover, the idea and possibility that the software could be used in autonomy by the patients, without the direct control and supervision of a clinician allows to think a future with more people receiving a valid program for

cognitive rehabilitation even if they are in their own home: with traditional paper and pencil tasks this is much less possible.

Lastly, given the flexibility and the variety of exercises and cognitive domains engaged by the Padua Rehabilitation Tool it was possible to deliver a cognitive rehabilitation to people with acquired brain injury. Although it was not conducted a randomized controlled trial, I collected on Chapter 6 some experiences of using the Padua Rehabilitation Tool on patients with acquired brain injury. In the specific, a briefly described a case of an early post-coma rehabilitation, a pilot study on patients after stroke, and two cases of cognitive rehabilitation after traumatic brain injury. The results obtained with these patients were certainly positive. In some cases, the cognitive improvement was seen and observed also in the neuropsychological assessment. In other cases, in particular in the most severe (e.g., Andrea), the benefits were more evident at the qualitative level. Surely, these results cannot be intended as solid conclusion of the efficacy of the PRT in patients with acquired brain injury. However, these results indicate that the Padua Rehabilitation Tool can be successfully used in different context and that can be adapted and tailored to the different needs of patients. Furthermore, the cases presented highlighted the advantage of using a mobile touch-screen when it is needed to deliver a cognitive intervention in peculiar context, such an intensive care unit, or when the rehabilitation is addressed to patients with motor impairment and hemiparesis on the dominant side.

Surely, in addition to the demonstrated efficacy of the Padua Rehabilitation Tool with people with dementia and to the promising efficacy with people with acquired brain injury, the results presented in this dissertation are useful for the understanding of the improvements that can be done in the next future to the software. First of all, it should be implemented an adaptive approach in changing the difficulty within and between the exercises. Now, the software provides a fixed training: each exercises has different levels of difficulty, but the steps are always the same for each patients. The key attribute of any adaptive training program is that it can make inferences about the learner's knowledge and can then adapt the training process to best accommodate the trainee's current learning needs (Fisk et al., 2009). The use of an adaptive computer-based program to continuously adjust task difficulty and maintain an appropriate level of challenge basing on current performance could be an excellent way for tailoring the training to the needs and competence of each single subject (Cicerone, 2012; Olesen, Westerberg, & Klingberg, 2004).

Furthermore, the Padua Rehabilitation Tool needs an interface within the software for a complete view of the performance with plots and statistics for each subject. Now, even if all the performances are recorded in a local database, the data are not available for patients or clinicians. The only ways for looking at the performance over time for each subject at each exercise are (1) importing the database in an ad-hoc software that I developed using MATLAB® (MathWorks, Inc., Natick, USA),

the "PRT - Data View", or (2) using a third-party software for importing the database (e.g., Microsoft Excel). Surely, one big advantage of new technologies is the capacity for an immediate processing and analysis of data. Moreover, it is important for both patients and clinicians an access to the data recorded, viewing the evolution overtime. Then, using as example similar software, it is important to implement a "data viewer" within the same Padua Rehabilitation Tool.

Furthermore, the entire score system of Padua Rehabilitation Tool should be revised. Presently, for each exercises are recorded different parameters, but there is not a unique score for each domain. The exercises are not organized in a progression of estimated difficulties and there is not provided a score that allow comparisons within and between exercises. For this reason, it was not possible to statistically investigate the strength of the relationship between the performance over time to the computer-based exercises and the standardized test scores proposed and studied in the chapter 3. Similar to the app investigated in Chapter 3 ("Constant Therapy"), the score system of Padua Rehabilitation Tool should be revised providing a progression order within each domain and a normalized score.

Lastly, thanks to the results obtained and discussed in this dissertation, I think that can be started a commercial plan for releasing the software to the public. Similar to other software the availability of the software in a large scale can accelerate the collection of new data that can be constantly used for testing the efficacy of the software. Indeed, are needed controlled trials for examining the efficacy of Padua Rehabilitation Tool in the rehabilitation of patients with cognitive impairments resulted from stroke, traumatic brain injury or brain tumor.

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Appendix 1

Screenshots of Padua Rehabilitation Tool

❖ Login, Menu, and language domain Menu

ESERCIZI COGNITIVI

NOME

ACCEDI

CG

HT Lab

ATTENZIONE

CONTROLLO MOTORIO

MEMORIA

ORIENTAMENTO

LINGUAGGIO

RICONOSCIMENTO

RAGIONAMENTO LOGICO

ESCI

LINGUAGGIO

ORDINE ALFABETICO   L'INIZIALE

COMPLETA LA PAROLA   L'INIZIALE 2

CREA LA PAROLA   SINONIMI

SILLABE   CONTRARI

INTRUSO

MENU

❖ Feedback

BENE	RIPROVA	L'ESERCIZIO E' FINITO	L'ESERCIZIO E' FINITO
☺	☹	☺	☹
TOCCA	TOCCA	TOCCA	TOCCA
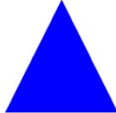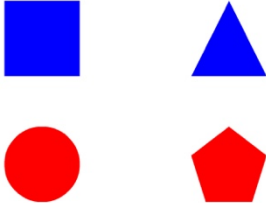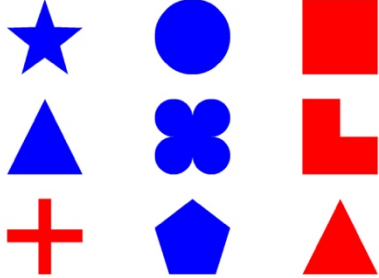
❖ Attention: **Quanti (How many?)**

SCEGLI LA VERSIONE

LIBERO

TEMPO

SCEGLI UN OGGETTO

MATITA   FIORE

MELA   LAMPADINA

ESCI

CONTA TUTTE LE LAMPADINE

POI TOCCA AVANTI

AVANTI

ESCI   AVANTI

ESCI   AVANTI

QUANTE ERANO LE LAMPADINE?

1   2   3

4   5   6

7   8   9
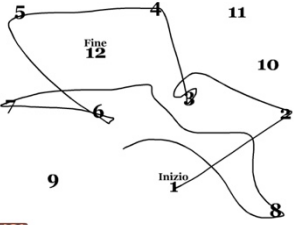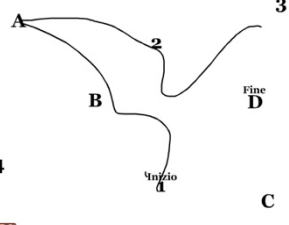
❖ Attention: **Go/No go**

Scegli la difficoltà

FACILE   DIFFICILE

Numero di stimoli: 30

FeedBack immediato? SI   NO

Durata degli stimoli

400 ms   800 ms   1 sec.   2 sec.   3 sec.

Variabile colore? SI   NO

ESCI   AVANTI

TOCCA SOLO QUANDO VEDI:

ESCI   AVANTI   ESCI

❖ Attention: **Detect**
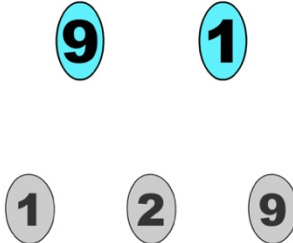
❖ Attention: **TMT**

❖ Memory: **Interferenza (Interference)**

❖ Memory: **Digitspan**

❖ Memory: **Cosa c'era (What was?)**

ANALIZZA LA SCENA

POI TOCCA GLI OGGETTI CHE ERANO PRESENTI

ESCI   AVANTI

ESCI   AVANTI

❖ Memory: **Che oggetto era? (What was the object?)**

LEGGI LE PAROLE

POI TOCCA LE IMMAGINI UGUALI ALLE PAROLE

ELEFANTE

ESCI   AVANTI

ESCI

❖ Memory: **Memory**

TROVA LE COPPIE DI IMMAGINI

ESCI   AVANTI

ESCI

ESCI

❖ Memory: **Memory – Sound**

TROVA LE COPPIE DI SUONI

ESCI   AVANTI

ESCI

ESCI

❖ Memory: **Pattern**

RIPETI LA SEQUENZA CHE TI VIENE MOSTRATA

3		
	4	
	1	2

ESCI   AVANTI

ESCI

ESCI

❖ Language: **Ordine alfabetico (Alphabetic order)**

ORDINA LE LETTERE:		E	P	R	E	P	R	E	P	R

(Note: figure with letter grids)

ORDINA LE LETTERE:

dalla A alla Z   dalla Z alla A

E	P	R		E	P	R		E	P	R
O	N	V		O	N	V		O	N	V
G	H	B		G	H	B		G	H	B
Z	D	C		Z	D	C		Z	D	C

ESCI   ESCI   ESCI   ESCI

❖ Language: **Completa la parola (Complete the word)**

COMPLETA LA PAROLA CON UNA DELLE ALTRE PRESENTATE

SENO

PIANO …

FORTE

BARI …

CENTRO
GENTE
URTI
CANE
NEVE
GRANO

ESCI   AVANTI   ESCI   ESCI

❖ Language: **Crea la parola (Create the word)**

TOCCA LE SILLABE CHE COMPLETANO LA PAROLA

LA
SA …
PI

CA
LI …
MA

BO
LI …
MA…   RE

ESCI   AVANTI   ESCI   ESCI   ESCI
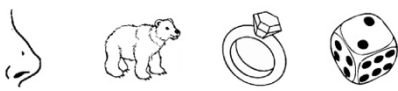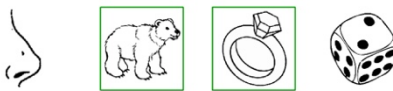
❖ Language: **Sillabe (Syllables)**

SCEGLI LA SILLABA CHE COMPLETA LA PAROLA

BO
PA …   MO
STA

SCEGLI TUTTE LE SILLABE CHE COMPLETANO LA PAROLA

TI …
PI   LA
STA   PA

ESCI   AVANTI   ESCI   ESCI   AVANTI   ESCI   AVANTI

❖ Language: **Intruso (Intruder)**

TROVA LA PAROLA "INTRUSA"

QUADRATO
SCATOLA
RETTANGOLO
TRIANGOLO

ESCI   AVANTI   ESCI

❖ Language: **L'Iniziale (Initial)**

❖ Language: **L'Iniziale 2 (Initial 2)**

❖ Language: **Sinonimi (Synonyms)**

❖ Language: **Contrari (Antonyms)**

❖ Logic Reasoning: **Denaro (Money)**
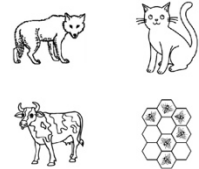
❖ Logic Reasoning: **Stime di denaro (Money estimates)**

❖ Logic Reasoning: **Sequenze (Sequences)**

❖ Identification: **Suoni (Sounds)**

❖ Identification: **Oggetti – 1 (Objects 1)**
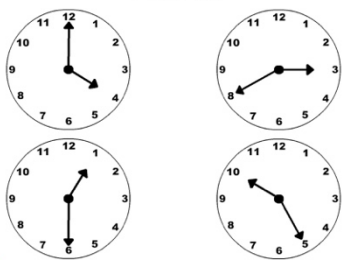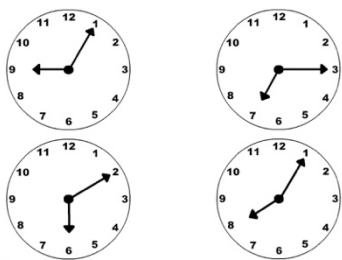
❖ Identification: **Oggetti – 2 (Objects 2)**

RICONOSCI GLI OGGETTI MOSTRATI	AQUILA ARANCIA BICCHIERE	AQUILA ELEFANTE PERA GATTO MARTELLO POLTRONA PINZE DIVANO
ESCI AVANTI	ESCI	ESCI

❖ Identification: **Rotazioni (Mental rotation)**

TOCCA LA FIGURA UGUALE A QUELLA MOSTRATA		
ESCI AVANTI	ESCI	ESCI
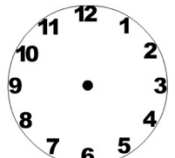
❖ Orientation: **Orario (Clock)**

	10:25	18:10
TOCCA L'OROLOGIO CHE INDICA L'ORARIO SCRITTO IN ALTO		
ESCI AVANTI	ESCI	ESCI
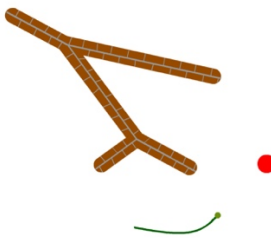
❖ Orientation: **Cerca il gatto (Find the cat)**

	Indica il gatto a sinistra della vasca	Indica il gatto nero sopra la mensola	Indica il gatto grande nero sopra il tavolo
TOCCA IL GATTO CHE SI TROVA NELLA POSIZIONE RICHIESTA			
ESCI AVANTI	ESCI	ESCI	ESCI
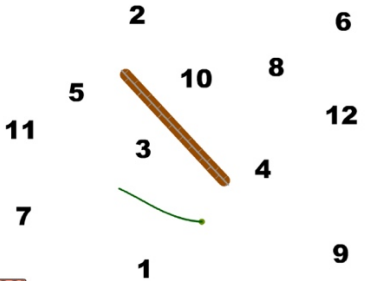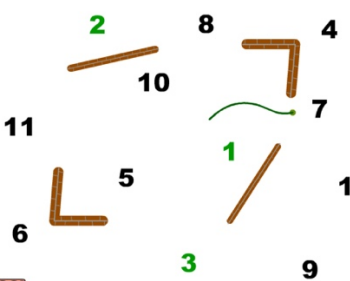
❖ Orientation: **Metti le lancette (Put the hands in the clock)**

	01:20	23:20
TOCCA I NUMERI DELL'OROLOGIO PER POSIZIONARE LE LANCETTE SULL'ORARIO RICHIESTO POSIZIONA PRIMA LA LANCETTA DELLE ORE E POI QUELLA DEI MINUTI		
ESCI AVANTI	ESCI	ESCI CANCELLA

139
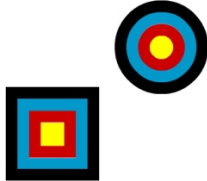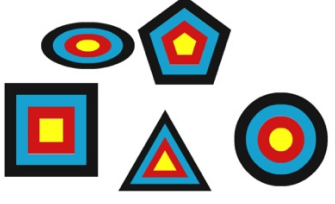
❖ Motor Control: **Snake**

❖ Motor Control: **Snake 2**
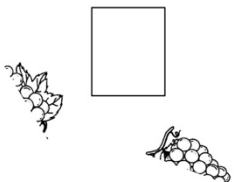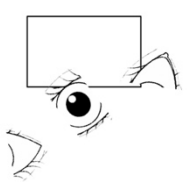
❖ Motor Control: **Bersaglio (Target)**

❖ Motor Control: **Bersaglio 2 (Target 2)**

❖ Motor Control: **Completa la forma (Complete the picture)**