UNIVERSITÀ DEGLI STUDI DI PADOVA

UNIVERSITY OF PADOVA

Department of Cardiac, Thoracic and Vascular Sciences

Ph.D. COURSE IN: Medical, Clinical and Experimental Sciences

CURRICULUM: Neurosciences

XXIX CYCLE

NUMERICAL ACTIVITIES OF DAILY LIVING (NADL) AND NUMERICAL ACTIVITIES OF DAILY LIVING – FINANCIAL (NADL–F) IN NEUROLOGICAL DISEASES

Coordinator: Ch.mo Prof. Gaetano Thiene

Supervisor: Ch.mo Prof. Carlo Semenza

Ph.D. Candidate: Francesca Burgio

To My Father…

ABSTRACT

What is the impact of acalculia upon an individual's everyday life? In clinical practice, a few measures of Activities of Daily Living are available. In these batteries, however, numerical abilities were not distinguished from other abilities. As a consequence, no instrument has been made available so far to measure the nature and the extent of damage to everyday life specifically brought by acalculia in a given individual. The first aim of this series of studies was to build and validate an instrument, the Numerical Activities of Daily Living (NADL), designed to measure this impact. The first section of the thesis describes the psychometric properties of the newly created NADL and the specific profiles observed among patients suffering of several neurological diseases (a specific study was devoted to neurofibromatosis type 1) by using this instrument; patients with a right hemisphere focal lesion were also the object of a specific study). A further development of NADL (NADL-Children) was built for the assessment of numerical activities of daily living in children: it helped to predict math school performance after the first year of primary school.

In the second section we deepened one particular aspect of daily living activities requiring numbers (i.e. dealing with finances) found to be critical in our studies employing NADL. Indeed, the loss of financial capacity can have serious legal, economical, and personal consequences on an individual. Therefore, we additionally created a tool (Numerical Activities of Daily Living-Financial; NADL–F) that was also successfully validated in clinical populations in Italy as the second scope of this thesis. We also explored the differences in financial and numerical domains between MCI and healthy controls by means of NADL and NADL–F. The cognitive domains found to be involved in the deficit may be appropriate targets for future intervention studies aimed at preserving functional independence in individuals with MCI. Finally we also correlated the performance in the NADL and NADL–F test with anatomical brain changes. The investigation of the neural correlates of financial and other daily numerical abilities will help us to better define the knowledge of this high-level functions; moreover the neuroimaging studies will shed light on the

brain areas related to the performance in financial tasks, and will be useful to find out the predictors of the time-course of decline in financial capacities.

TABLE OF CONTENT

INTRODUCTION

Formal mathematics apparently concerns a daily topic concerning a few professional sectors (e.g. engineering, physics). However we all use numbers for numerous activities of daily living such as counting, measuring, comparing, putting things in order, etc. Moreover, we constantly need to calculate, understand fractions, proportions and ratios, and to understand and remember PIN codes, telephone numbers, addresses, shoe sizes, and so on.

In the past two decades, neuroscience has made a significant progress in the understanding of how the brain represents numerical information and sustains mathematical computation (Butterworth & Walsh, 2011). One of the main sources of evidence has been the observation of patients, with acute, stable or progressive brain damage that gives rise to a range of specific disorders of number processing and calculation, usually referred to as “acquired acalculia” (Hécaen & Angelergues, 1961; Semenza, 2008; Ward, 2015; Willmes, 2008).

Despite the quantity of studies on acalculia, the impact of such important disturbances on an individual's everyday life is still unclear. Deterioration of mathematical abilities is a very frequent consequence of brain damage, however, and a socially relevant one. In the elderly, even in healthy ones, slowing of arithmetical functions is found, which is often clinically hard to distinguish from that produced by neurological deterioration (Zamarian, Stadelmann, et al., 2007). Moreover, slowing of numerical skills with age may have many causes, not just degenerative diseases; thus evaluating this deterioration will be preliminary to effective retraining.

Research with brain-damaged patients has repeatedly demonstrated a range of quite specific deficits. For example, there may be selective deficits in number transcoding from spoken to written numbers, or from written to spoken numbers, arithmetical signs, arithmetical facts and rules, arithmetical procedures and conceptual knowledge have been shown to be selectively disrupted after brain damage (see for reviews Butterworth, 1999; Cipolotti & van Harskamp, 2001; Semenza, 2008; Semenza, Grana, & Girelli, 2006). For instance, some patients were unable to use numbers in the Arabic code but could use the alphabetical code (Cipolotti, Butterworth, & Warrington, 1994).

Patients may also be found with impairments in one type of operation and not in others, such as addition but not multiplication, or subtraction but not addition (Cipolotti & van Harskamp, 2001). Some of these cases are prima facie counterintuitive, like the case of sparing of division relative to multiplication (Venneri & Semenza, 2011). Impaired math skills can coexist with apparently normal reasoning and language. Cipolotti et al. (1991) thus described the case of a lady, CG, who, after a left parietal lobe damage, was still proficient in language tasks and reasoning, but could not deal at all, verbally or otherwise, with numbers above four.

Specific error patterns and relative weaknesses may be a signature of specific neurological pathologies (see Cappelletti, Butterworth, & Kopelman, 2012; Palmieri et al., 2013, for reviews). For instance, Delazer et al. (2006) found that in Posterior Cortical Atrophy, number comparison, approximation and number transcoding were severely impaired, but multiplication, addition facts and rules were preserved; likewise Palmieri et al. (2013) recently found that in Amyotrophic Lateral Sclerosis the largest majority of errors were in multiplication tasks.

Although these studies answered some important questions, they did not directly address the issue of how a specific deficit relates to the range of tasks that a patient can or cannot do in his or her everyday life. To take one example, Patient CG (Cipolotti et al., 1991) was a competent book keeper and manager of the family hotel, but as a consequence of a focal brain lesion, suffered very severe global acalculia, despite her otherwise spared cognitive skills, and therefore could no longer maintain her previous occupation. Patient BE (Hittmair-Delazer, Semenza, & Denes, 1994), an accountant, and patients ZA and TL (Girelli, Delazer, Semenza, & Denes, 1996), all relatively young people, could go back effectively to the pre-morbid occupation or studies only when they were specifically treated for their very selective arithmetical facts retrieval deficits. It seems likely that the different specific deficits could impact in different ways on daily living, though this has up till now not been investigated.

The aims of the thesis:

1. Clinical tools

The primary aim of this project was to build and validate instruments to differentiate different types of acquired (and developmental) acalculia, as a precondition for assessing the effects of these deficits on everyday life. The underlying hypothesis is that these impairments go beyond what can be inferred from the available scales evaluating activities of daily living in general, and are not adequately captured by measures of the general deterioration of cognitive functions as assessed by standard clinical instruments.

The first section of the thesis describes the psychometric properties of the newly created numerical activities of daily living (NADL) instrument, and the specific profiles observed among patients suffering of several neurological diseases by using this instrument (**Study 1**).

In order to provide a tool for investigating numerical activities in daily living in developmental age a further tool, NADL–Children was prepared, that assesses the influence of the richness of numerical environment on a child's scholastic achievements in math (**Study 5**).

In the second section, we deepened one particular aspect of daily living activities requiring numbers (i.e. dealing with finances) found to be critical in our studies employing NADL. Therefore, we additionally created a tool (Numerical Activities of Daily Living – Financial; NADL–F) which was also successfully validated in clinical populations in Italy (**Study 6**). The loss of financial capacity can have serious consequences on the individual; this might be related to significant changes in the person's psychological condition, and questions the person's individual autonomy, which is fundamental for wellbeing. Legally, a person that is judged as unable to look after his/her own finances and estate is often assigned a financial guardian. Impairments in financial abilities encountered in this part of the population may also be a risk to society. For all these reasons, evaluation of an individual's ability to manage financial matters is needed.

2. Applications in neurological diseases and developmental populations

It is now well-established that different degenerative diseases show characteristic impairment profiles which follow particular lesional/degeneration patterns, such as in the case of Alzheimer disease (Carlomagno et al., 1999; Delazer, Karner, Proell, & Benke, 2006; Halpern, McMillan, Moore, Dennis, & Grossman, 2003; Martini, Domahs, Benke, & Delazer, 2003; Zamarian, Semenza, Domahs, Benke, & Delazer, 2007), Parkinson disease and other basal ganglia dysfunctions (Benke, Delazer, Bartha, & Auer, 2003; Delazer et al., 2004; Tamura, Kikuchi, Otsuki, Kitagawa, & Tashiro, 2003; Zamarian et al., 2006, 2009), semantic dementia (Cappelletti, Butterworth, & Kopelman, 2001; Cappelletti et al., 2012), amyotrophic lateral sclerosis (Palmieri et al., 2013), and genetic defects (Bertella et al., 2005; Semenza et al., 2008, 2012). Each degenerative disease seems to affect aspects of number processing and calculation in a distinct way.

It is interesting to show deficits in cognitive functions in a neurological population when the anatomo-clinical correlation allows to identify specific neural circuits sustaining specific tasks/functions or when it is possible to characterize a specific pattern of behaviour for which specific remediation strategies can be developed. A finding can also become interesting when a dissociation of functions (some spared vs some impaired) is defined. In some cases deficits in calculations are compensated when applied to more ecological situations.

In this project, we examined the scholastic tasks and everyday activities related to numbers in three populations of patients: people who suffered right brain damage, patients diagnosed with mild cognitive impairment (MCI), and patients with a genetic condition affecting numerical performance: Neurofibromatosis type 1. Additionally, we evaluated the effects of exposing children to numerical activities early in life, as a means to evaluate possible beneficial effects on the acquisition of formal scholastic knowledge throughout the lifespan.

The aim of the study on right brain damaged patients (**Study 4)** was twofold: on the one hand, it was designed to shed light on the specific role of the right hemisphere in calculation and the specific localization of different functions underlying formal numerical skills. On the other hand it was conceived to provide information regarding the localization of functions underlying more complex functions required in ecological tasks which, we hypothesized, involve areas other than those traditionally associated with numerical representations. Moreover, this study was justified by the fact that although a number of previous studies had investigated different aspects of number and calculation processing (Basso, Burgio, & Caporali, 2000; Dahmen, Hartje, Büssing, & Sturm, 1982; Hécaen, 1962; Hécaen & Angelergues, 1961; Jackson & Warrington, 1986; Rosselli & Ardila, 1989), only some of them studied right-hemisphere damaged patients and their deficits in specific numerical and calculation domains. Crucially, the reason(s) why right hemisphere acalculic patients err the most, and, in particular, which features of their calculation deficit should be considered "spatial" or secondary to visuo-spatial functions was still unclear since no previous study focused on this specific aspect. Last but not least, this study provided a first indication of the impact of numerical disorders on the RHD patients' everyday life. Such information is crucial for building up appropriate rehabilitation programs that directly impact everyday activities of the patients. In particular, the study of numerical abilities on this category of patients also evidenced a highly specific pattern of errors which was explored in a further study. The study highlighted the role of the right hemisphere (specifically the right insula and possibly also the right parieto-frontal connections) for transcoding complex digits, particularly those containing zeros. It was argued that right hemisphere-damaged patients struggle with the transcoding of zeros in complex numbers due to their difficulties in setting-up appropriate empty-slot structures, and in the parsing and mastering of the categorical spatial relations between digits. These functions stand apart from other mechanisms necessary for completing transcoding tasks with other numbers, do not seem to be totally reduplicated in the left hemisphere (otherwise there would not be errors in such patients), and do not entirely depend on generic processing resources. The results of this study, although highly innovative, will not be included in the main body of the thesis because they did not concern numerical abilities of daily living. However, for the sake of completeness, they are presented in Appendix C.

We were aware of the fact that not every function associated with the performance of numerical abilities of daily living would be localized in circumscribed areas of the brain, but rather could activate distributed networks. Thus, in **Study 2**, we attempted to identify these networks and the different neuropsychological functions that support the patients' performance on NADL. The Study recruited MCI patients and age- and education-matched controls. The comparison of the brain volumes associated with performance in both populations advanced our understanding of the networks supporting ecological numerical abilities both in healthy and pathological aging.

Study 3 examined the numerical performance in a special population with Neurofibromatosis type 1, a genetic condition affecting mathematical abilities since early childhood. Applying a clinical test for studying numerical abilities in adults with NF1, for the first time, enlightens the interaction between a specific cognitive deficit, the trajectory of the genetic disease, and possible compensatory mechanisms to overcome the deficit throughout the lifespan. Indeed, even though children with NF1 show substantial deficits in mathematics (Levine, Materek, Abel, O'Donnell, & Cutting, 2006), the characterization of mathematical abilities in adults with NF1 and its impact on the patients' everyday life had received no attention in the previous literature.

We anticipated at least three possible outcomes evidenced by the NADL battery: a) Given the numerical deficits characterizing the psychological profile in NF1 children, and the frequently reported continuum between childhood and adulthood in certain cognitive domains (Descheemaeker, Plasschaert, Frijns, & Legius, 2013; Uttner, Wahlländer-Danek, & Danek, 2003), numerical deficits could be a common feature also among NF1 individuals in adulthood and, as a consequence, the daily activities requiring numbers could be also impaired in this group of patients b) Lifespan activities (e.g. schooling, shopping, etc.) and brain plasticity might re-establish calculation deficits observed in childhood, at least partially, in adults c) Functional and ecological measures might dissociate in adulthood, possibly due to the fact that ecological tasks often require less abstraction than isolated mathematical computations. Abstraction appears to be particularly difficult for NF1 due to reduction of their executive functions. The latter possibility also finds support in a previous study of Payne and colleagues which found that the performance of NF1 patients in ecological tasks is often inconsistent with their scores in neuropsychological tests. In particular, the authors showed deficits in attention and executive deficits in children with NF1, but no consistent relationships between the cognitive tests and the functional outcomes (Payne, Hyman, Shores, & North, 2011).

This section closes by extending the study of numerical abilities of daily living to normally developing children (**Study 5**). In particular, we hypothesized that indirect numerical exposure (i.e. informal activities within the family environment and numerical information learned at home) enhances the children's representational systems underlying mathematical performance. We reasoned that evaluating abstract arithmetic abilities (e.g., 1 + 3 = ?) in pre-school children might provide an incomplete measure of their early mathematical intuitions because children are generally unfamiliar with formal terms such as "plus," "minus," or "equals" before entering school. Measuring the same abilities applied to everyday situations (e.g., if you have one banana and I give you three more, then how many bananas do you have now?) should provide a clearer view of the children arithmetic intuitions and the way they interact with the numerical exposure received at home. The predictive value of home exposure to numbers on later scholastic achievement is also one aim of this study.

The second section of the thesis focuses on one specific practical domain associated with everyday functioning: financial competence. Financial competence is defined as "the capacity to manage money and financial assets in ways that meet a person's needs and which are consistent with his/her values and self-interest" (Lichtenberg, Qualls, & Smyer, 2015). In **Study 6** we developed a novel instrument, NADL–F, to assess financial capacity in clinical populations, with the primary aim of providing a psychometrically valid tool to be used and adapted in a European environment. NADL–F comprises basic monetary skills, such as counting coins, the ability to shop and make mental calculations while shopping, the ability to manage home bills, and the ability to detect fraud. NADL–F thus mainly includes performance-based tasks that simulate real life situations.

Finally, in **Study 7**, we also correlated the performance in the NADL–F test with anatomical brain changes and specific neuropsychological profiles in MCI patients and healthy controls. We chose to begin evaluating the NADL–F in MCI patients who are very likely to show first signs of cognitive decline and to suffer a great loss of independence consequent to the FA impairment. These patients have been recently shown to experience problems in tasks tapping financial capacities such as financial conceptual knowledge, bank statement management and bill payment (Griffith et al., 2003, 2010; Marson et al., 2009; Okonkwo, Wadley, Griffith, Ball, & Marson, 2006; Sherod et al., 2009). Moreover, the FA decline in such patients can give rise to legal issues such as financial abuse and exploitation (Marson et al., 2000).

CHAPTER I

Study 1: A new clinical tool for assessing numerical abilities in neurological diseases: numerical activities of daily living

(Published in Frontiers in Aging Neuroscience, 2014, Vol. 6)

INTRODUCTION

Number processing and calculation are an essential part of our culture. We use numbers for counting, measuring, comparing, putting things in order, etc. Moreover, we constantly need to calculate, understand fractions, proportions and ratios, and to understand and remember PIN codes, telephone numbers, addresses, shoe sizes, and so on. Of course, many occupations need relatively high levels of numerical skill, and poor skills will have an adverse effect on life chances in education and employment, indeed a larger effect than poor literacy skills, as a large-scale cohort study in the UK demonstrates (S. Parsons & Bynner, 2005).

In the past two decades, neuroscience has made a significant progress in the understanding of how the brain represents numerical information and sustains mathematical computation (Butterworth & Walsh, 2011). One of the main sources of evidence has been the observation of patients, with acute, stable or progressive brain damage that gives rise to a range of specific disorders of number processing and calculation, usually referred to as “acquired acalculia” (Hécaen & Angelergues, 1961; Semenza, 2008; Ward, 2015; Willmes, 2008).

Despite the many studies of the neural basis of typical and atypical mathematical abilities the impact of such important disturbances on an individual's everyday life is still unclear. Deterioration of mathematical abilities is a very frequent consequence of brain damage, however, and a socially relevant one. In the elderly, even in healthy ones, slowing of arithmetical functions is found, which is often clinically hard to distinguish from that produced by neurological deterioration (Zamarian, Semenza, et al., 2007). Moreover, slowing of numerical skills with age may have many causes, not just degenerative diseases and evaluating this deterioration will be preliminary to effective retraining.

Research with brain-damaged patients has repeatedly demonstrated a range of quite specific deficits. For example, there may be selective deficits in number transcoding from spoken to written numbers, or from written to spoken numbers, arithmetical signs, arithmetical facts and rules, arithmetical procedures and conceptual knowledge have been shown to be selectively disrupted after brain damage (see for reviews Butterworth, 1999; Cipolotti & van Harskamp, 2001; Semenza, 2008; Semenza et al., 2006). For instance, some patients were unable to use numbers in the Arabic code but could use the alphabetical code (Cipolotti et al., 1994). Patients may also be found with impairments in one type of operation and not in others, such as addition but not multiplication, or subtraction but not addition (Cipolotti & van Harskamp, 2001). Some of these cases are prima facie counterintuitive, like the case of sparing of division relative to multiplication (Venneri & Semenza, 2011). Impaired math skills can coexist with apparently normal reasoning and language. (Cipolotti et al., 1991) thus described the case of a lady, CG, who, after a left parietal lobe damage, was still proficient in language tasks and reasoning, but could not deal at all, verbally or otherwise, with numbers above four.

Specific error patterns and relative weaknesses may be a signature of specific neurological pathologies (see for reviews Cappelletti et al., 2012; Palmieri et al., 2013). For instance, (Delazer, Karner, Zamarian, et al., 2006)found that in Posterior Cortical Atrophy, number comparison, approximation and number transcoding were severely impaired, but multiplication, addition facts and rules were preserved; and (Palmieri et al., 2013)recently found that in Amyotrophic Lateral Sclerosis the largest majority of errors were in multiplication tasks.

It seems likely that the different specific deficits could impact in different ways on daily living, though this has up till now not been investigated. The instrument we are developing here can provide the foundation for such an investigation.

In one specific practical area, financial competence, there have been attempts to assess the impact of cognitive difficulties more generally on everyday life. Marson and co-workers provided a theoretical framework and appropriate tools to assess reduced financial competence in the elderly and in pathological conditions such as Alzheimer's disease, MCI or traumatic brain injury (Dreer, DeVivo, Novack, & Marson, 2012; Marson et al., 2000, 2009; Martin et al., 2012). Studies by Webber and colleagues have focussed on the legal aspect of numerical competence, that is, whether an individual requires an administrator to manage some or all of his or her financial affairs, and to this end have developed the Financial Competence Assessment Inventory (FCAI) (Webber, Reeve, Kershaw, & Charlton, 2002). For people with cognitive impairment (classified as acquired brain injury, dementia or psychiatric disorders), a positive correlation was found between the Arithmetic score on the WAIS-III and FCAI, an assessment scale of financial competence (Kershaw & Webber, 2008).

However, although these studies answered some important questions, they did not directly address the issue of how a specific deficit relates to the range of tasks that a patient can or cannot do in his or her everyday life. To take one example, Patient CG was a competent bookkeeper and manager of the family hotel, but as a consequence of a focal brain lesion, suffered very severe global acalculia, despite her otherwise spared cognitive skills, and therefore could no longer maintain her previous occupation. Patient BE (Hittmair-Delazer et al., 1994), an accountant, and patients ZA and TL (Girelli et al., 1996), all relatively young people, could go back effectively to the pre-morbid occupation or studies only when they were specifically treated for their very selective arithmetical facts retrieval deficits. The main aim of this study is to build and validate an instrument, the numerical activities of daily living (NADL), designed to differentiate different types of acquired acalculia, as a precondition for assessing the effects of these deficits on everyday life. We then sought to address the following questions:

- To what extent do these specific impairments relate to the difficulties measured by available scales evaluating activities of daily living in general (e.g., Instrumental Activities of Daily Living, IADL, Katz, 1983; Lawton & Brody, 1969)?
- To what extent does general deterioration of cognitive functions as measured by standard clinical instruments like the MMSE capture numerical deficits?

1.1. METHODS

Four new instruments were specifically designed for this investigation, and were administered to participants along with known clinical batteries.

1.1.1. THE NADL BATTERY

The way NADL is structured allowed us to collect information about the degree of awareness of the deficit by the patient and by her or his caregivers.

NADL is divided into four parts (for details, see Appendix A and Supplementary Material 1).

I. The Patient Interview (Since this study involves a control group, the Patient Interview is referred to as the Participant Interview).
II. The Caregiver Interview.
III. The Informal Test, which is designed to offer a brief clinical assessment to determine whether the Formal Test of numerical abilities needs to be administered.
IV. The Formal Test. This is a detailed assessment of the numerical abilities critical to daily living; these abilities are typically assessed in neuropsychological investigation of numerical and mathematical impairments. Thus, this test may be considered as an external criterion for the other subtests. In clinical practice, this only needs to be administered if there is evidence

in the first three parts indicating a deficit in numerical abilities. However, for this study, it was always administered in order to evaluate the validity of the first three parts.

Parts 1 and 2: Participant interview and caregiver interview

These brief interviews, administered separately to the patient and to the caregiver, are meant to provide a rough assessment of the patient's awareness about his or her numerical deficit. The comparison of the patient's answers with those of the caregiver is designed to provide such information. These interviews consist of 10 simple questions (e.g., “Do you shop by yourself?”; “Do you make your own telephone calls unaided (i.e. do you dial them yourself)” on how well the participant uses numbers in everyday life, with equivalent questions asked of the participant and, in reference to the participant, of the caregiver. The activities were selected as relevant activities of daily living that are likely to be influenced by numerical abilities on the basis of previous literature and of clinical experience (frequent complaints about what patients cannot do any more and similar information).

Part 3: The informal test of numerical competence

This test is meant to assess the numerical competence likely to be necessary in everyday life. It encompasses questions in the domains of Time (current date?), Measure (amount of pasta or rice in an average portion?), Transportation (distance between home and hospital?), Communication (own telephone number?), General Knowledge (days in a week?) and Money (cost of a car?). When the question implied an estimate rather than a precise number, the answers was considered correct if within a reasonable quantity interval (e.g., amount of pasta/rice: 80 g ±50 per person), The choice of these domains was made in consideration of previous literature and available instruments (Katz, 1983; Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963; Lawton & Brody, 1969). These domains (mostly chosen on the basis of most frequent patients' own complaints and those of their relatives) do not, of course, exhaust the range of tasks that might involve numerical abilities in the life of the participant. However, they can indicate potential difficulties in everyday life justifying further clinical assessment of mathematical functions.

Part 4: The formal test of numerical abilities

This battery has been designed to assess the numerical abilities of patients using brief graded-difficulty subtests. The battery is organized in four sections consistent with previous neuropsychological batteries for numerical abilities (Delazer, Girelli, Granà, & Domahs, 2003).

Section 1: Number comprehension

This section comprises three subtests that test the patient's ability to relate number words and digits to numerical magnitudes: Numerosity Comparison (Comparing the number of squares in two panels presented simultaneously, up to nine squares per panel), Number Line marking (The participant is asked to mark a number on a line defined by its end points), and Digit Comprehension (10 panels, similar to the above, are presented one at a time along with a list of digits 1 to 10. For each panel, the participant points to the appropriate number).

Section 2: Reading and writing Arabic numeral

The aim of this section is to assess the ability to transcode between written and spoken numbers. This section is separate from that on calculation, since a dissociation has been observed in individual patients (Cipolotti & van Harskamp, 2001). The section consists of two subtests: Reading Numbers Aloud (including two digits, e.g. 12, up to five digits, e.g., 65300, numbers), and Writing Numbers on Dictation (including two digits up to five digits numbers).

Section 3: Mental calculation

The aim of this section is to assess the ability to perform simple mental calculation (on spoken presentation). This section consists of three subtests: Mental Addition (e.g., 5 + 7), Mental Subtraction (e.g., 13 − 4), and Mental Multiplication (e.g., 9 × 6).

Section 4: Written calculation

This section assesses in detail the components of calculation. The section consists of six subtests grouped in two subsections. The first subsection, named Understanding Arithmetical Rules and Principles, assesses the ability to use basic rules (e.g., operations with 0) and principles (e.g., the commutativity of addition) in written form. It consists of subtests for Arithmetical Rules (e.g., 0 + 9; 1 × 7), Addition Principles (e.g., 26 + 37 = 63 → 37 + 26 = ?), and Multiplication Principles (94 × 5 = 470 → 93 × 5= ?). The second subsection assesses the ability to perform more complex operations in writing. This latter subsection, named Written Operations consists of three subtests: Addition (e.g., 463 + 659), Subtraction (548 − 231), Multiplication (429 × 53).

1.1.2. Materials

Mini Mental Scale Examination (MMSE)

The MMSE (Mini-Mental-State Examination, Folstein, Folstein, & McHugh, 1975) is the most widely used instrument to quickly evaluate the extent of general mental deterioration.

Montreal Cognitive Assessment (MoCA)

The MoCA (Montreal Cognitive Assessment, Nasreddine et al., 2005) is a brief screening tool, more recent and slightly longer and more sensitive to Mild Cognitive Impairment (MCI) than MMSE. For this reason it was added to the most widely used MMSE.

Instrumental activities of daily living (IADL)

The IADL (Instrumental Activities of Daily Living, Katz, 1983; Lawton & Brody, 1969) is a widely used scale, originally built in the attempt to assess everyday functional competence, that taps a level of functioning not captured by the more commonly used Activities of Daily Living scale (Katz et al., 1963). This scale collects information from the patient's caregiver about a series of functions concerned with a person's ability to cope with her/his environment in terms of familiar tasks: Use of the telephone; Shopping; Food Preparation; House Keeping; Laundry; Mode of Transportation; Responsibility for own Medication; Ability to Handle Finances. Importantly, some of these activities entail the use of numbers and calculation.

1.1.3. Participants

A total of 323 volunteer participants took part in the study: a control group (n = 148) and a patient group (n = 175).

Participants of the control group were recruited in Italy. They were autonomous in their activities of daily living and, at the time of the assessment, they had no pathologies that could have influenced their cognitive status or its assessment. They had no record of developmental learning disorders. This group had a mean age of 53.05 years (*SD* = 16.80, range = 21–94), a mean education of 11.16 years (*SD* = 4.47, range = 5–26). Eighty-one were female.

Data from the control group were used to obtain normative cut-offs and some data from the control group were also included in the analysis assessing the psychometric properties of the battery.

Participants in the patient group were mostly recruited at the I.R.C.S.S. San Camillo on the Venice Lido or in the Policlinico of Padova. They gave their informed consent according to the Helsinki Declaration. The diagnosis of these patients was established through the standard protocols for their pathologies. The patient group had a mean age of 58 years (*SD* = 18.01, range = 18–90) and a mean education of 10.371 years (*SD* = 4.35, range = 2–19). Eighty-nine were female.

Details on demographic variables and neurological diagnosis of the patient group are reported in **Table 1.1**. Data from several different groups of patients were included for two reasons. First, to obtain variance in test scores in order to meaningfully assess the properties of the batteries (the control groups was expected to score at ceiling in most of the tests); second, to allow a preliminary investigation comparing specific profiles in numerical and math deficits in different neurological diseases.

Table 1.1 | Demographic variables of the patient group.

Diagnosis	Age mean (SD)	Education mean (SD)	Gender as number of female (percentage of female)	N
Alzheimer	74.07(7.81)	8.69(4.85)	8(61%)	13
Mild cognitive impairment	75.08(7.81)	8.75(3.85)	15(42%)	36
Parkinson	64.82(9.07)	10.75(4.91)	13(46%)	28
Multiple sclerosis	51.28(13.25)	10.67(3.87)	32(53%)	60
Neurofibromatosis type1	28.40(9.18)	12.64(3.98)	13(59%)	22
Cortico basal degeneration	73(-)	5(-)	1(50%)	1
Fronto temporal dementia	65(-)	13(-)	0(0%)	1
Lewy body dementia	76(-)	17(-)	0(0%)	1
Left hemisphere lesion	56(13.07)	11(4.86)	5(71%)	7
Righ themisphere lesion	67(1.71)	11(5.31)	1(25%)	4
Amyotrophic lateral sclerosis	65(2.83)	5(-)	1(50%)	2
Overall patients	58.23(18.01)	10.37(4.35)	89(51%)	175

Age and education are reported as number of years. The Gender column indicates the number of female participants. N indicates the number of participants in the group.

1.1.4. Procedure

All participants were tested individually. Testing was administered by trained neuropsychologists, always in the following order: first the Participant Interview, followed by the Informal test and then by the Formal test. The Caregiver Interview was administered to a caregiver or to a close relative of the patient, in the patient group, at a separate time. Additionally, the Caregiver Interview was also administered to a relative of normal controls, even though it was expected that almost all of these reports would be at ceiling.

Together with the NADL battery, all participants were administered with MMSE and MoCA. The caregiver was also asked to compile the IADL.

All statistical analyses were performed with the free statistical software R (R Development Core Team, 2012).

1.2. Results

1.2.1. Psychometric Properties

Several psychometric properties of NADL were investigated. To limit the extent of ceiling effect, this analysis was performed only on patients.

Internal consistency was calculated by means of standardized Cronbach's alpha. The consistency of the whole formal test was satisfactory, with a Cronbach's alpha of 0.73. The consistency of each subtest was also evaluated. The average of Cronbach's alpha was 0.59. Numerosity comparison and number line showed the highest Cronbach's alpha (0.8 and 0.78, respectively), while writing number to dictation and reading number aloud showed the lowest Cronbach's alpha (0.37 and 0.19, respectively). All results are reported in **Table 1.2**. The very low scores on some subtests are not surprising, since in these tests even patients' performance was almost at ceiling. However, we decided to keep these tests because NADL is designed for patients with neuropsychological disorders: some patients may therefore show specific impairments and variability in those subtests, even if our sample of neurological patients performed at ceiling. Notably, low consistency was observed only in tests showing performance almost at ceiling.

Table 1.2 | Reliability of NADL.

	Cronbach's alpha	Test–retest reliability	Inter-rater reliability
Interview with patients	0.5	0.69	0.82
Interview with caregiver	0.62	0.98	1
Informal total	0.64	0.86	0.94
Formal total	0.73	0.86	0.87
Numerosity comparison	0.8	0.51	0.84
Number line	0.73	0.50	0.60
Digit comparison	0.71	0.32	0.9
Reading number aloud	0.37	0.20	0.68
Writing numbers on dictation	0.19	0.24	0.2
Mental addition	0.7	0.28	0.58
Mental subtraction	0.5	0.44	0.95
Mental multiplication	0.61	0.72	0.92
Written rules	0.59	0.38	0.55
Written addition	0.65	0.68	0.81
Written multiplication	0.63	0.46	0.62
Written operations – addition	0.6	0.60	0.66
Written operations – subtraction	0.71	0.50	0.83
Written operations – multiplication	0.6	0.38	0.55
Total number comprehension	0.43	0.34	0.78
Total reading and writing Arabic numerals	0.39	0.39	0.62
Total mental calculation	0.58	0.76	0.93
Total rules and principles	0.78	0.88	0.92
Total written calculation	0.74	0.47	0.68

The Table reports reliability scores for NADL.

Test–retest reliability was assessed in a subsample of 19 participants, from the sample of patients with a neurological disease. All participants were tested within a month interval between the two observations. A Spearman correlation was utilized as an index of test–retest reliability. The test–retest reliability of the single subtests ranged from 0.20 to 0.98. As in the case of Cronbach's alpha, the low values in some subtests are a consequence of the scores almost at ceiling observed in the sample considered. These results, rather than indicating a low reliability, indicate that the large majority of participants performed at ceiling in both test and retest; the few participants that departed affected the results, given the relatively small score range of the subtests. These data should be taken into account when using those tests in the assessment of change in the ability of the patient due to recovery, intervention or both.

The ***Inter-rater reliability*** of NADL was assessed by means of Intra-Class correlations (ICC) on a subset of 14 patients. Two examiners separately scored their performance. The ICC was very high in almost every test, supporting a high objectivity (that is, independence from subjective judgments in attributing the scores) of the overall battery.

1.2.2. Cut-offs

Cut-off scores based on the distribution of scores in the healthy participant group were calculated. Cut-offs were calculated separately for each subtest of the formal test and for the informal test, but also for each section of formal and informal test, and for the global scores of formal and informal tests. To account for the effect of demographic variables (age, education, and gender) on cut-offs we used the results of regressions with the subtest or test scores as dependent variables and the demographic variables as predictors (the analysis are reported in detail in the paragraph age and education effects). The residuals of the regression models built can be conceived as adjusted scores, i.e., what remains of the observed scores after the effects of demographic variables are removed. Cut-offs were calculated as 5th percentile of adjusted scores in the control sample, for those tests in which a significant effect of demographic variable was found. The advantage of a regression method approach is that it allows using the whole normative sample to have a single cut-off for each score (and not cut-offs stratified for age, education and gender). Before comparing an observed subtest or test score with a cut-off, the effect of demographic variables is removed (if significant), utilizing the same regression model that was used to obtain the cut-offs, with the following procedure: first a predicted score of the participant is calculated by entering his/her values for the relevant demographic variables (age, education, and gender) in the regression model obtained on the control group sample **Table 1.3** then, the predicted score is subtracted from the observed score to obtain the residual, that is the adjusted score for that given participant. If a demographic variable shows no effect on a score, than there is no reason to take into account that variable in calculating the cut-offs. In such case the cut-offs were calculated as 5th percentile of the raw scores. A spread sheet reporting cut-offs is provided in Supplementary Material 1. This file, once entered with a patient's data, automatically shows if the score is below cut-off in each subtest.

1.2.3. Construct validity of the test

Since NADL is the first battery with the aim of assessing the impact of numerical deficits in daily living, we cannot use external evidence of actual daily living to assess its validity. However, it is possible to collect evidence on the construct validity of the test by investigating correlations among test sections and among the tests and other external tests. Thus, we inspected the correlation among the parts of NADL and with the other tests administered to investigate if the results support the claim that the parts of NADL are indeed measuring the construct of numerical activities related to numbers. Importantly, the formal test of NADL can be considered as an external criterion for the other parts, since it covers the main domains of neuropsychological models of mathematical and numerical abilities, and it closely resembles other existing batteries (see for example, Delazer, Girelli, et al., 2003).

The results of correlations on NADL global scores and scores on subtests are reported in **Table 1.4**. Since data from the Caregiver Interview were not available for all the participants, the data of these correlations come from a subset of 141 participants for whom this data was available, evenly distributed among control participants and neurological patients. All statistical analyses reported in this paragraph included this sample of healthy controls and patients.

Table 1.3 | Regression models for cut-off corrections of NADL global scores and scores on subtests.

	Intercept (*SE*)	Age (*SE*)	Education (*SE*)	Gender (*SE*)	R^2
Interview with patients	10.57(0.21)	−0.02(0.004)	—	—	—
Interview with caregiver	—	—	—	—	—
Informal total	23.38(0.49)	−0.05(0.008)	—	—	0.18
Formal total	70.78(2.45)	−0.10(0.03)	0.39(0.11)	—	0.26
Numerosity comparison	—	—	—	—	—
Number line	—	—	—	—	—
Digit comprehension	—	—	—	—	—
Reading number aloud	4.08(0.13)	—	0.04(0.01)	0.20(0.09)	0.11
Writing numbers on dictation	—	—	—	—	—
Mental addition	—	—	—	—	—
Mental subtraction	—	—	—	—	—
Mental multiplication	4.45(0.22)	—	0.07(0.02)	—	0.09
Written rules	6.27(0.38)	−0.02(0.004)	0.07(0.02)	—	0.30
Written addition	3.42(0.44)	−0.02(0.005)	0.07(0.02)	—	0.25
Written multiplication	4.66(0.21)	−0.02(0.004)	—	—	0.21
Written operations – addition	—	—	—	—	—
Written operations – subtraction	6.49(0.27)	−0.02(0.004)	—	—	0.13
Written operations – multiplication	—	—	—	—	—
Total number comprehension	—	—	—	—	—
Total reading and writing Arabic numerals	9.54(0.17)	—	0.06(0.01)	0.25(0.12)	0.14
Total mental calculation	15.96(0.35)	—	0.09(0.03)	—	0.05
Total rules and principles	13.74(0.85)	−0.05(0.01)	0.17(0.04)	—	0.40
Total written operations	17.02(0.54)	−0.04(0.01)	—	—	0.11

Each row in the table reports the coefficients of one linear regression model. The first column reports the dependent variable, the following four columns report the parameter for the models (the value within brackets indicates the standard error for the parameter). The last column reports the adjusted R−squared. A missing value in the table indicates that the parameter did not contribute significantly to the model fit and then was removed in the modelling procedure. All coefficients reported (with the exception of Intercept, which is always included in a meaningful model) were selected by mean of backward elimination of non−significant variables. All variables reported significantly improved the fit of the model and their associated t−values had $p < 0.05$.

Table 1.4 | Correlation between NADL and other tests.

	Interview with patient	Interview with caregiver	Informal total	Formal total	MMSE	MoCA
Interview with caregiver	0.82					
Informal total	0.47	0.58				
Formal total	0.54	0.64	0.65			
MMSE	0.60	0.74	0.65	0.75		
MoCA	0.46	0.61	0.51	0.58	0.74	
IADL	0.73	0.81	0.51	0.57	0.65	0.54

All correlations showed in **Table 1.4** *are significant at $p < 0.001$ ($n = 141$). The participants included in these correlations were both healthy controls and patients with neurological diseases.*

The overall pattern of correlations suggests a source of communality that may underlie the interrelation among scores on the different tests. This is not surprising, because all of the tests are supposed to be influenced by the overall cognitive status of the individual.

These results thus support the construct validity of NADL and suggest that the interview with the caregiver is a better estimate of numerical abilities than the interview with the patient.

1.2.4. Awareness of numerical deficits in neurological patients

The interviews with the participant and with the caregiver give the opportunity to estimate the numerical competence in the life of the patients. Results of the correlations suggest that the estimate of the caregiver on the impact of numerical deficits in daily living is better than the estimate made by the patients themselves (see previous paragraph). The error bias in patients was further explored by comparing the scores on the interviews by means of paired t-tests. For this analysis control subjects and patients were analysed separately, since control subjects mostly scored at ceiling in the interviews. The analysis on control subjects showed no difference between the interview with the participant and the interview with their relative [$t = 0.469$, $df = 77$, $p = 0.64$]. The analysis of patients showed a significant difference, with higher scores in the patient interview compared with the caregiver interview [$t = 4.41$, $df = 62$, $p < 0.001$]. In summary, the patients tend to overestimate their abilities as compared to the judgment made by the caregivers.

1.3. Discussion

The main purpose of this study was to obtain an instrument able to assess numerical activities of daily living. The instrument described here, the NADL battery, has been normed on a sufficient number of participants, including control participants varying in the age, and its psychometric properties have been tested on participants affected by a wide variety of pathological conditions.

We have found that the NADL battery shows a good reliability both in terms of test-retest and inter-rater reliability. The internal consistency was satisfactory as well. Construct validity was also satisfactory, as tested by the correlation between NADL parts and cognitive status as assessed by MoCA and MMSE, and with IADL. Importantly, the Patient Interview and Caregiver Interview correlated well with IADL, and with the Informal and Formal parts. The Caregiver Interview was a better predictor of actual numerical ability, with additional finding that the Patient Interview overestimated numerical abilities. This confirms the NADL strategy of using these interviews as a brief clinical screening tool to see whether a more detailed investigation of the patient's numerical abilities is indicated.

Since patients tended to overestimate their own numerical competence, a specialized numerical battery, such as NADL, can be employed to evaluate numerical competence for financial or legal decisions about the ability of an individual to manage his or her own affairs, especially financial affairs. The need of such evaluation is likely to increase with the elderly, irrespective of clear neurological damage (Webber et al., 2002).

It is known that distinct patterns of numerical deficits have been identified for a number of neurological conditions, including progressive diseases, such as Alzheimer's disease, Temporal Lobe Epilepsy, Fronto-temporal Dementia, Semantic Dementia and other forms of Primary Progressive Aphasia, Amyotrophic Lateral Sclerosis, Posterior Cortical Atrophy, Parkinson's

Disease and other diseases of basal ganglia (see Palmieri et al., 2013 for a review) and genetic defects (Turner Syndrome, Bruandet, Molko, Cohen, & Dehaene, 2004; Prader Willi Syndrome, Semenza et al., 2008, X Fragile Premutation, 2012). These studies have been conducted with different assessment tools and with patients with differential severity of numerical deficit. The pathological profile obtained in these studies depends on a combination of the effect on damage on specific neural networks, and also on the type of test that has been used and by the overall degree of cognitive deficit. It is thus hard to compare these studies with each other, because the outcome of each individual study might heavily depend on type of test, degree of severity and other factors like, in particular, age and education that may vary widely. In future, the standardized use of battery such as NADL will enable clinicians and researchers to compare the numerical abilities and disabilities in different conditions more systematically.

In our study, we were able to compare for the first time on the same battery Parkinson's Disease and Multiple Sclerosis. On Total Written Calculation, patients with Parkinson performed worse than patients with Multiple Sclerosis, irrespective of the severity of the condition, general cognitive impairment, age or education. Similarly, neurofibromatosis, a pathological condition for which no previous investigation of numerical abilities was available, and where the pathology shows much earlier than in the above-mentioned degenerative diseases, is characterized by a distinct profile of numerical deficits, especially mental calculation, again independently from severity of the disease, age, and education.

NADL may also be useful in the assessment of "cognitive or brain reserve" the resilience of function in the context of neural damage (see, for example, Nucci, Mapelli, & Mondini, 2012). It has been widely claimed that high educational level acts as a protective factor, and here we can test the more specific prediction of whether a high level of mathematical education level protects against slowing or deterioration of mathematical abilities with aging and disease.

The NADL battery is an initial step in developing an efficient assessment tool. A shorter version of the Formal part may be needed. However, the detailed and extensive investigation presented here provides the basis on which to proceed. Subsequent analysis of the data from patients and controls may eventually enable us to include only the most discriminating items, and thereby reduce the length of the battery. Importantly, however, the interview with the caregiver seems to provide a first, rough but quite reliable, estimate of a patient's numerical skills. It may thus be used when a thorough evaluation cannot be done, or to guide a screening decision.

The present battery enables the investigation of the consequences of a given numerical defect on numerical activities of daily living. This is work in progress. Factors such as the influence of relative severity will be the focus of subsequent studies. At the present stage, however, this battery can already be employed in its present form to assess patients for their rehabilitation or retraining and to monitor and assess the outcome of rehabilitation and retraining in a real life setting.

Study 2: Anatomical substrates and neurocognitive predictors of daily numerical abilities in mild cognitive impairment

(Published in Cortex, 2015, Vol. 71)

2.1. INTRODUCTION

Deficits in mathematical abilities contribute to the difficulties experienced by patients with mild cognitive impairment (MCI) in everyday life activities (Nygard, 2003; Winblad et al., 2004). For instance, MCI patients have been recently shown to experience problems in understanding numerical information concerning health care (Delazer, Kemmler, & Benke, 2013; Pertl et al., 2014). Moreover, impairments in tasks tapping financial capacities such as financial conceptual knowledge, bank statement management and bill payment have been also reported in these patients (Griffith et al., 2003, 2010; Okonkwo et al., 2006; Sherod et al., 2009).

The numerical deficits in MCI may be primary or secondary to other cognitive difficulties. (Griffith et al., 2003), in particular, related financial impairments to deficits in executive functions. Similarly, (Zamarian, Stadelmann, et al., 2007; Zamarian, Semenza, et al., 2007) found that executive dysfunctions affect the patients' performance even on basic mathematical tasks. In particular, the studies of Zamarian and colleagues found that MCI patients who score within the normal range on basic arithmetic assessments show difficulties on arithmetic applied to daily-life by having to recruit additional, non-numerical resources. Accordingly, further studies have emphasized the relevance of age-associated attentional and executive decline in ac-counting for numerical difficulties in the elderly (Cappelletti, Didino, Stoianov, & Zorzi, 2014; Duverne & Lemaire, 2005; Lemaire & Arnaud, 2008). These studies have conjectured that such decline plays a role in those everyday numerical problems that show the typical features of a multistep problem, i.e., requiring focused attention, planning, reasoning and monitoring of the solution procedure.

One interesting question is whether the mathematical difficulties experienced by MCIs are the result of specific regional anatomical changes. The hypothesis of the present study is that, if previously learned mathematical concepts and facts are deteriorating in MCI, then age-related compensatory mechanisms and functional reorganization might increasingly be more salient. Thus, for instance, a shift from parietal to frontal functioning, for which there is existing evidence in aging (Lövde, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010) is expected, independently of whether these changes lead to effective compensation. Such functional reorganization is likely to reflect increasing load on frontal executive functions. Parallel deterioration of linguistic and visuospatial abilities might also modulate this process. In order to investigate these neural changes, the present study will explore the pattern of association between numerical abilities assessed with neuropsychological instruments, and volumetric properties of the brain, both in patients diagnosed with MCI and in healthy controls.

Between-group qualitative differences in these maps would provide a rationale for the presence of both subjective and objective impairment of numerical processing in the MCI population.

2.2. METHODS

2.2.1. PARTICIPANTS

Sixty-two elderly adults were invited to undertake a comprehensive clinical, neuropsychiatric, and neuropsychological examination at the IRCCS San Camillo Hospital (Lido-Venice, Italy). After completing a full neurological and neuropsychological assessment, participants were divided in two groups according to the Petersen et al., criteria for diagnosing MCI (Petersen et al., 2001). Thirty-three participants were diagnosed as having MCI (20 males), and twenty-nine (11 males) were enrolled in the control group because they showed no sign of cognitive impairment. Other sources of cognitive impairment such as focal lesions were ruled out by visual inspection of MRI scans, carried out by an experienced neuroradiologist. All participants were right-handed and none of them had a history of psychiatric disorder, drugs or alcohol abuse. There were no significant differences between MCI patients (M = 9.5 y, SD = 4.3) and the control group (M = 11.1 y, SD = 4.7) in scholastic attainment estimated in years of education (p > .05). Significant differences between the two groups were instead found in age t(60) = 3.83, p < .001, d = .98 (controls M = 67.1 y, SD = 8.4; MCI M = 74.4, SD = 6.0) and in the Mini Mental State Examination scores [MMSE (Folstein et al., 1975) t(60) = 5.23, p <.001, d = 1.31; controls M = 29.1, SD = 1.3; MCI M = 26.5, SD = 2.5]. As a consequence, these two variables were included as covariates in all analyses. Written informed consent was obtained from all participants after the nature of the study was fully explained. The study was approved by the Institutional Review Board of the IRCCS Fondazione Ospedale San Camillo (Venice, Italy).

2.2.2. Measures

Cognitive assessment

A comprehensive neuropsychological battery was administered to all participants as part of their clinical evaluation. This battery included measures of attention, executive functions, reasoning, language, memory, and visuospatial abilities. The tests used to assess each domain (See Supplementary Material 2) were chosen on the basis of theoretical and clinical considerations. The aim was to obtain cognitive profiles which could be clinically informative and sensitive to the impact of early-stage neurodegeneration.

Numerical assessment

All participants completed three sub-sections of the Numerical Activities of Daily Living test-NADL (Semenza et al., 2014). NADL measures the impact of specific numerical abilities on participants' everyday life. The sub-sections administered to the participants included:

1) A brief Interview with the participant, which assesses the patient's awareness of their possible numerical deficits in everyday life. This interview consists of ten simple questions enquiring

about how well the participant uses numbers in everyday life. (e.g., "Do you shop by yourself?"; "Do you make your own telephone calls unaided, do you dial them yourself?")

2) An Informal test that measures the participants' numerical competence in everyday tasks. It encompasses questions in the domains of Time (e.g., current date), Measure (e.g., amount of pasta or rice in an average portion), Transportation (e.g., distance between home and hospital), Communication (e.g., own telephone number), General Knowledge (e.g., number of days in a week?) and Money (e.g., estimating the price of a new car).
3) A Formal Test of Numerical Abilities, which assesses the patients' scholastic numerical abilities using brief sub-tests graded for difficulty. It includes the following domains: Number comprehension, Transcoding (reading and writing Arabic numerals), Mental calculation, Knowledge of rules and principles of calculation, and Written operations.

Number comprehension comprises three subtests that assess the patient's ability to relate number words and digits to numerical magnitudes: Number line marking (the participant is asked to estimate the position of a number on a line defined by its endpoints), Numerosity comparison (comparing the number of squares in two displays presented simultaneously, up to nine squares per panel), and Digit comprehension (ten displays are presented one at a time along with a list of digits from 1 to 10. For each display, the participant is requested to point at the corresponding number).

Transcoding consists of two sub-tests: Reading Numbers Aloud (including two-digit numbers, e.g., 12, up to five-digit numbers, e.g., 65,300), and Writing Numbers to Dictation (including two-digit up to five-digit numbers).

Mental Calculation encompasses three subtests: Mental Addition (e.g., 5 + 7), Mental Subtraction (e.g., 13 - 4), and Mental Multiplication (e.g., 9 × 6).

Knowledge of Arithmetical Rules and Principles assesses the ability to use basic rules (e.g., the commutativity of addition, or managing operations with 0) in written form. It consists of subtests of Arithmetical Rules (e.g., 0 × 9; 1 × 7), Addition Principles (e.g., if 26 + 37= 63 then 37 × 26= ?), and Multiplication Principles (if 94 × 5 = 470 then 93 × 5 =?).

Written Operations included complex Addition (e.g., 463 + 659), Subtraction (548 - 231), and Multiplication (429 × 53).

2.2.3. Statistical analysis of behavioural data

Non-parametric Wilcoxon rank-sum tests were used to assess continuous variables, including the clinical, demographic, and performance scores in the NADL battery. In an initial analysis, the scores of the two groups in the three sub-sections of the NADL were compared setting Bonferroni's correction for multiple comparisons (alpha = .01). In a second analysis, each domain of the Informal and Formal assessments was compared between groups, adjusting the significance level according to the number of comparisons carried out within each sub-section (alpha = .008). Additionally, given that the two groups differed in age (see Section 2.2.1), a further Pearson's correlation analysis was carried out to evaluate the association between age and scores on each sub-test and domain of the NADL battery.

Finally, participants' raw scores on the neuropsychological tests were converted into z scores and averaged to form the composite variable representing each cognitive domain (see Supplementary Material 2 for additional details). The neuropsychological composites were entered into separate stepwise regression models to determine the cognitive correlates of numerical abilities showing between-group differences. The use of composite scores allowed us to reduce sensibly the risk of multicollinearity and potential instability of single variables.

2.2.4. MRI acquisition, pre-processing and analysis

Three-dimensional (3D) T1-weighted MR images were acquired using a 1.5 T Philips Achieva MRI system with a Turbo Field Echo sequence. Voxel dimensions were 1.1 × 1.1 × .6 mm and the field of view was 250 mm with a matrix size of 256 × 256 × 124. In addition, a T2-weighted axial scan and a coronal fluid attenuated inversion recovery (FLAIR) scan were also acquired to detect the presence of significant vascular pathology or micro bleeds, which might either be not compatible with the diagnosis of MCI prodromal to AD or induce a suboptimal segmentation of the T1-weighted images. A number of pre-processing steps were followed to obtain the gray matter (GM) and white matter (WM) segments from the 3D T1-weighted structural scan before carrying out statistical analyses using SPM8 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK). To correct for global differences in brain shape, structural images were warped to a standard stereotactic space and segmented to extract maps of GM, WM and cerebral spinal fluid using the default segmentation procedure available in SPM8 (Ashburner & Friston, 2005). Modulated-normalized GM and WM images were then smoothed with an 8 mm FWHM Gaussian kernel to reduce variability between participants. Smoothed-modulated-normalized segments were entered into voxel-based multiple regression analyses to investigate linear correlations between GM and WM volumes and participants' scores on each sub-test of the NADL battery. Moreover, a factorial model was used to characterize the relationship between numerical abilities, diagnostic group and brain volumes. For this purpose the participants' performance on each NADL sub-test was turned into a categorical value using the median split method. Then, a 2 × 2 ANOVA with performance (below the median and above the median) and group (MCI and Controls) as in-dependent variables was carried out to determine the main effect of group and the interactions. Age, years of education, MMSE scores, and total intracranial volume values were included as covariates in both the regression and the factorial models. Height threshold was set at $p < .001$ (uncorrected) for all analyses. Only cluster corrected areas (FWE) with a significance level of $p \leq .05$ and at least 200 voxels are reported. Anatomical regions were identified using the Talairach Daemon Client (Lancaster et al., 2000), following conversion of the Montreal Neurological Institute coordinates extracted from the SPM output into Talairach coordinates using the Matlab function mni2tal (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach).

2.3. Results

2.3.1. Behavioural results

A summary of the performance of the two groups on the NADL sub-sections and their corresponding domains is presented in **Table 2.1**. The first set of analyses comparing the scores of the two groups in the three NADL sub-sections (total scores) showed no significant differences between the groups in the Interview ($Z = 2.02$, $p = .043$), but there were significant differences in the Informal ($Z = 3.55$, $p = .0003$) and Formal assessments ($Z = 3.50$, $p = .0004$). The subsequent set of analysis carried out on the domains of the Informal Numerical competence test showed that MCI patients and controls significantly differed in Time estimation ($Z = 2.82$, $p = .004$) and Money Usage ($Z = 2.58$, $p = .007$). The same set of analysis carried out in the domains of the Formal test showed significant differences between the groups in Number comprehension ($Z = 3.05$, $p = .002$), Transcoding ($Z = 3.13$, $p = .001$), Logic and Principles ($Z = 3.45$, $p = .0005$) and Written operations ($Z = 2.54$, $p = .007$). No other domain showed significant group differences (all ps > .008). Additionally, there was no correlation between age and the participants' scores on the NADL's sub-tests and domains.

2.3.2. Neurocognitive modelling of numerical abilities in MCI

The stepwise regression in which the Informal assessment of the NADL was the dependent variable settled on a final model that comprised language and visuo-spatial abilities as predictors. Measures of long-term memory predicted Time estimation, while the model for Money usage included visuo-spatial abilities and abstract reasoning as predictors.

Patients' visuo-spatial abilities, executive functions and abstract reasoning emerged as significant predictors of performance in the Formal assessment. For Number comprehension the only predictor was visuo-spatial abilities, while language abilities predicted the patients'

Table 2.1 | Summary of behavioural results.

	Interview with patient (max. 10)
	Mean (SD)
MCI	8.7 (1.6)
Healthy Controls	9.4 (1.0)

	Informal test of numerical abilities						
	Mean (SD)						
	Time estimation (max. 5)	**Measure (max. 1)**	**Transportation (max. 1)**	**Communication (max. 1)**	**Semantic knowledge of numerical information (max. 7)**	**Money usage (max. 8)**	**Total score (max. 23)**
MCI	4.0 (.9)	.8 (.4)	.6 (.5)	.8 (.4)	5.6 (.8)	6.5 (1.7)	18.4 (3.0)
Healthy Controls	4.5 (.7)	1.0 (.0)	.8 (.4)	.9 (.2)	6.0 (.8)	7.3 (.8)	20.8 (1.5)

	Formal test of numerical abilities							
	Mean (SD)							
	Number comprehension (max. 19)	**Reading Arabic numerals (max.5)**	**Writing Arabic numeral (max. 5)**	**Mental Calculation (max. 18)**	**Knowledge of calculation rules (max. 7)**	**Logic and principles (max. 8)**	**Written Operations (max. 17)**	**Total score (max. 79)**
MCI	16.8(1.6)	4.4(.6)	4.6(.5)	16.2(2.1)	5.5(1.2)	4.7(2.1)	12.6(4.0)	64.9(9.3)
Healthy Controls	17.8(1.1)	4.8(.4)	4.9(.3)	17.2(1.0)	6.1(1.1)	6.5(1.4)	14.8(2.1)	72.2(4.8)

performance on the Transcoding tasks. Finally, abstract reasoning, visuo-spatial abilities, and executive functions and attention predicted the patients' performance on written operations. Abstract reasoning predicted also the performance on the Logic and principles tasks. All results are reported in **Table 2.2**.

Table 2.2 | Predictors of Performance on NADL domains of Participants with MCI.

NADL tests	Predictor	Coefficient of determination	*p*-value
Informal Assessment General Score	Language	1.361	.013
	Visuo-spatial abilities	.767	< .001
Time estimation	Long-term memory	.466	< .001
Money usage	Visuo-spatial abilities	.377	.002
	Abstract reasoning	.732	.012
Formal Assessment General Score	Executive functions	5.638	.020
	Visuo-spatial abilities	1.563	.007
	Abstract reasoning	4.528	< .001
Number comprehension	Visuo-spatial abilities	.597	< .001
Transcoding	Language	.557	< .001
Logic and principles	Abstract reasoning	2.519	< .001
Written operations	Executive functions and attention	3.304	.007
	Visuo-spatial abilities	.551	.049
	Abstract reasoning	1.362	.033

2.3.3. Neurocognitive modelling of numerical abilities in controls

Controls' abstract reasoning (β = .45; p =.02), and long-term memory abilities (β = .98; p = .008) predicted the performance on written operations [Model R^2 = .31, $F(1,28)$ = 5.39; p = .01]. No neuropsychological measures predicted the controls' performance on the remaining NADL sub-tests.

2.3.4. VBM RESULTS

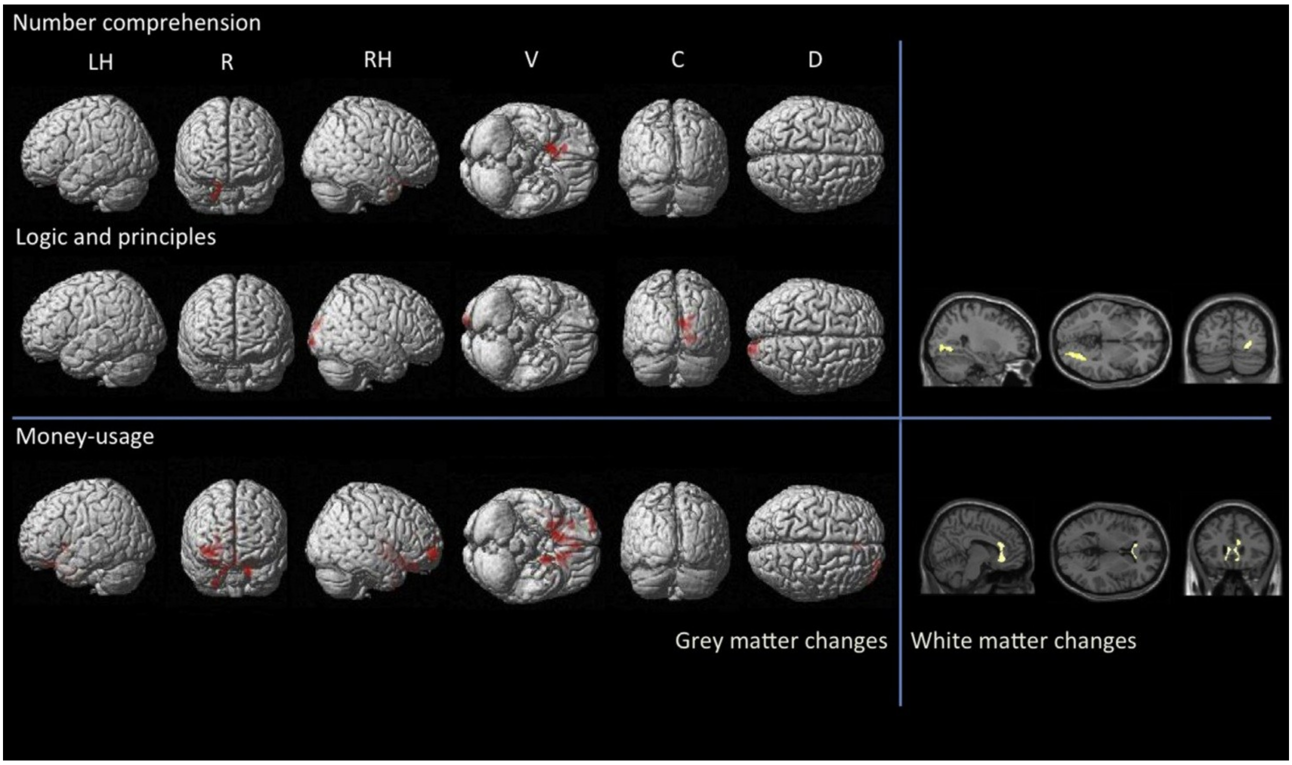
Voxel-based regression models

The NADL sub-tests and domains that showed significant between-group differences in the behavioural analyses were entered into separate regression models to evaluate the GM and WM volume correlations with the tests. Money-usage scores showed significant positive correlations with GM volume in the left mesial frontal cortex, right superior frontal cortex and right superior temporal areas in the MCI group. Total scores of the Formal test were significantly associated with GM volume values in the right middle occipital areas in the MCI group. Similarly, Number Comprehension and Logic and principles tasks showed significant positive correlations with GM volume in the right frontal gyrus and right occipital cuneus, respectively (see **Figure 2.1**). Logic and principles performance also correlated positively with volumetric changes of WM in the right occipital areas. Significant positive correlations between Money-usage and WM volume were also found in the sub-lobar, extra nuclear area of the corpus callosum. There were no significant correlations in other sub-tests and domains. No significant positive correlations between scores on any of the NADL measures and brain volumes (GM and WM) were found in the control group. Significant negative correlations between Money-usage and GM volume were found in the right-occipital, left-temporal and left-posterior cingulate. Similarly, Time estimation showed significant negative correlations with GM volume in the left-occipital and the proximity of the substantia nigra nuclei, in the right portion of the midbrain **Table 2.3** shows a summary of the findings.

Voxel-based factorial mode

This analysis, as the previous one, was carried out only on the NADL sub-tests and domains that showed significant between-group differences in the behavioural analysis. Significant GM volume reduction was detected in MCI patients with respect to healthy controls for the Transcoding sub-test in the left insula and Left Superior Temporal Gyrus. This difference was conspicuous between the high-performing sub-group of patients and the high-performing sub-group of controls. Moreover, in the Money-usage subtest a number of areas including the left/right Inferior Temporal Gyrus and left superior Temporal Gyrus showed a significant interaction between performance and group (**Table 2.4** and **Figure 2.2**): while controls differed according to the level of performance, such difference did not appear in MCI. No significant be-tween group differences or interactions were detected in any other subtests.

Figure 2.1 | Representative regions significantly correlated with the MCI group performance on specific NADL subtests.



The image is superimposed on a standard high definition T1 template. LH = left hemisphere; R = rostral view; RH = right hemisphere; V = ventral view, C = caudal view; D = dorsal view.

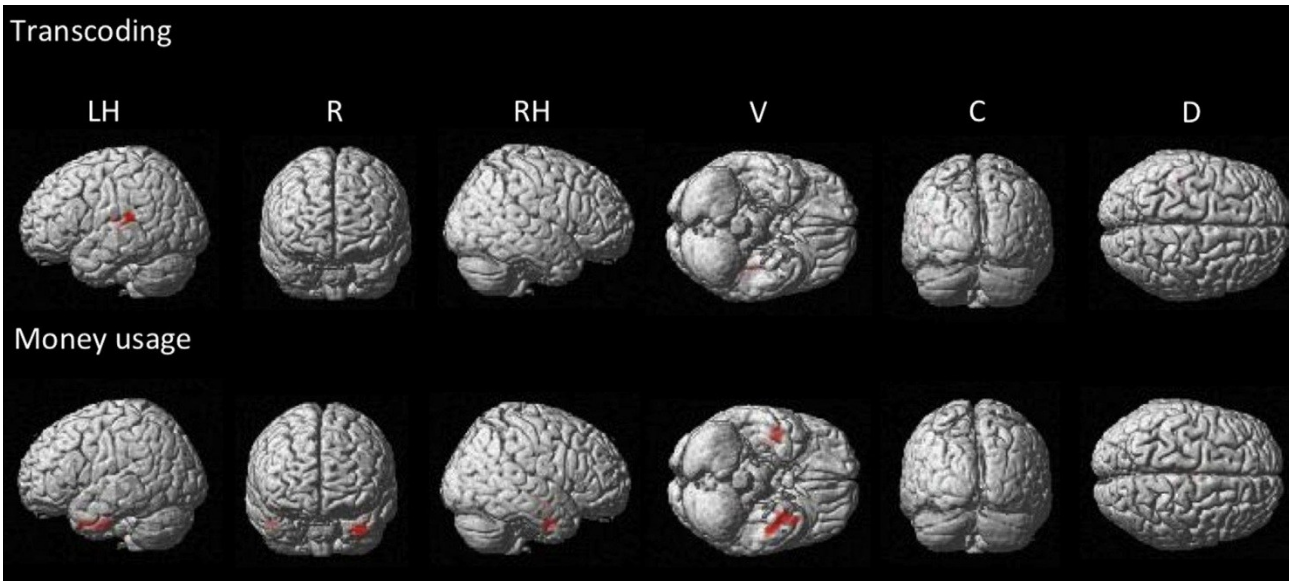
Table 2.3 | Correlations between GM and WM volume, and NADL scores.

	Group	Matter	Correlation	Number of voxels per cluster	Cluster level *p* value (uncorrected)	FWE corrected *p* value at cluster level	*Z* Value at local maximum	Talairach coordinates x	y	z	Brain region (Brodmann's area)
Informal test of Numerical Competence											
Money usage	MCI	GM	Positive	1031	<.001	<.001	4.38	28	6	−37	Right superior temporal gyrus (BA 32)
	MCI	GM	Positive	306	.001	.013	4.05	30	58	−10	Right superior frontal gyrus (BA 10)
	MCI	GM	Positive	446	<.001	.002	3.98	−12	18	−19	Left medial frontal gyrus (BA 25)
	MCI	GM	Positive	199	.006	.067	3.58	0	38	−17	Left medial frontal gyrus (BA 11)
	MCI	WM	Positive	243	.008	.029	3.60	−8	25	2	Corpus Callosum
	Control	GM	Negative	3722	<.001	<.001	4.73	14	−79	9	Right occipital cuneus (BA 17)
	Control	GM	Negative	1213	<.001	<.001	4.14	−44	−14	−9	Left-temporal sub-gyral (BA21)
	Control	GM	Negative	334	.005	.037	4.08	−18	−48	13	Left-posterior cingulate (BA30)
Time estimation	Control	GM	Negative	507	.001	.008	4.14	−20	−76	30	Left-occipital precuneus (BA 31)
	Control	GM	Negative	900	<.001	<.001	4.05	8	−12	−9	Right substantia Nigra
Formal test of Numerical Abilities											
General score	MCI	GM	Positive	504	<.001	.001	4.22	14	−89	15	Right middle occipital gyrus (BA 18)
Number comprehension	MCI	GM	Positive	348	.001	.008	4.18	18	5	−15	Right frontal-subcallosal gyrus (BA 34)

Table 2.4 | Significant effects at the voxel-based comparison between groups.

	Effect	Number of voxels per cluster	Cluster level *p* value (uncorrected)	FWE corrected *p* value at cluster level	*Z* Value at local maximum	Talairach coordinates x	y	z	Closest GM region (Brodmann's area)
Transcoding	Greater volume in Controls than in MCI patients	335	.007	.044	3.94	−36	−23	10	Left insula (BA13)
					3.74	−38	−30	16	Left Superior Temporal Gyrus (BA41)
Money Usage	Interaction: Controls differed as a function of their performance. MCI did not	294	.005	.037	3.93	6	−10	24	Right Cingulate Gyrus (BA23)
					3.67	−4	−24	33	Left Cingulate Gyrus (BA23)
					3.17	−10	−10	28	Left Caudate Body
		403	.001	.018	3.92	−46	−13	−30	Left Inferior Temporal Gyrus (BA20)
					3.82	−32	4	−30	Left Superior Temporal Gyrus (BA38)
					3.26	−40	14	−24	Left Superior Temporal Gyrus (BA38)
		407	.001	.018	3.90	44	−9	−30	Left Inferior Temporal Gyrus (BA20)
					3.67	38	−10	−15	Right Temporal Lobe (BA20)
					3.60	40	−21	−2	Right insula (BA13)
		393	.001	.018	3.79	−16	−45	1	Left parahippocampal Gyrus (BA30)
					3.52	−20	−37	−8	Left parahippocampal Gyrus (BA30)
					3.45	−18	−48	12	Left Posterior Cingulate (BA30)

Figure 2.2 | Representative regions evidencing significant differences and interactions between MCI patients and healthy controls.



The image is superimposed on a standard render of the brain. LH = left hemisphere; R = rostral view; RH = right hemisphere; V = ventral view, C = caudal view; D = dorsal view.

2.4. Discussion

Basic numerical abilities and their use in everyday life were found to be significantly poorer in MCI patients than in healthy controls. In contrast, no significant group difference was found in the score assessing awareness of numerical difficulties in everyday life. This is an important finding insofar as it shows that MCI patients, typically complaining about memory and naming difficulties (e.g., Joubert et al., 2010), do not express concerns about progressively deteriorating numerical skills. Such unawareness may exacerbate the patients' deficit, which heavily impacts on their daily life.

MCI patients do not experience difficulties in every numerical domain, however. Within basic abilities, only Number comprehension, Transcoding, applying logic and principles, and Written operations account for the difference with the control group. This finding might be possibly due to an overall higher level of difficulty of these particular tasks than other numerical tasks. Although the current data do not rule out this possibility, this interpretational avenue seems rather unlikely. In fact, if the intrinsic difficulty of the tasks were influencing the level of performance, one should expect that patients with other neurological conditions should also fail in this or in other similar tests. Rather, it is now well-established that different degenerative diseases show characteristic impairment profiles which follow particular lesional/degeneration patterns, such as in the case of Alzheimer disease (Carlomagno et al., 1999; Delazer, Karner, Proell, et al., 2006; Halpern et al., 2003; Martini et al., 2003; Zamarian, Semenza, et al., 2007), Parkinson disease and other basal ganglia dysfunctions (Benke et al., 2003; Delazer et al., 2004; Tamura et al., 2003; Zamarian et al., 2006, 2009), semantic dementia (Cappelletti et al., 2001, 2012), amyotrophic lateral sclerosis (Palmieri et al., 2013), and genetic defects (e.g., Bertella et al., 2005; Semenza et al., 2008, 2012). Each degenerative disease seems to affect aspects of number processing and calculation in a distinct way. Likewise, it is thus possible that the current findings also reflect a profile that specifically reflects the cognitive decline in MCI. The pre-sent study, however, is the first which has used the NADL to assess numerical competence; the specificity of this pattern can only be determined by comparing the pattern detected in this MCI sample with those of future studies with other populations tested using the same instrument.

Similarly, when numerical abilities are tested with everyday life tasks, only some tasks and not others seem to be affected in MCI. The domains that were found significantly impaired in the current study, i.e., Time estimation and Money usage, reflect activities that do not imply sophisticated financial knowledge (Griffith et al., 2003). These numerical activities seem the first to be disrupted by the mechanisms of neural deterioration usually present in cases of MCI. Since a pattern of association was found between these simple numerical abilities and composite measures of long-term memory and abstract reasoning, their early impairment in MCI seems to reflect the consequences of a decline in these fundamental cognitive abilities. In addition, the fact that Alzheimer's disease, the most likely neuropathological cause of MCI (Morris et al., 2001), is characterized by significant changes in these two cognitive domains is consistent with and corroborates this evidence. Moreover, the results obtained in the regression analyses suggest that compensatory/adaptative mechanisms may guide the performance of MCI patients on those NADL sub-tasks. In fact, the cognitive domains predicting performance in MCI were not predictive of the same ecological numerical capacities in the control group.

Data from the VBM analyses showed a pattern of significant brain structure correlation that can provide some clues about the anatomical areas supporting performance on the NADL in patients with MCI. Total scores of the Formal test, as well as those of Number Comprehension and Logic and Principles were significantly associated with GM volumes in the right occipital areas and right frontal gyrus. The evidence of a significant association emerging in frontal and occipital areas may reflect the need to recruit structures not traditionally associated with basic numerical skills such as the inferior parietal cortex (Arsalidou & Taylor, 2011; Dehaene & Cohen, 1995, 1997) to support performance on one of the most difficult tasks for MCI patients: Number comprehension. Frontal regions are normally involved in explicit reasoning; their recruitment might signify loss of automatic processing, and might reflect reversal to a more effortful (and ineffective) elaboration of this type of stimuli, while, on the other hand, the association with volumes in occipital regions might reflect a widespread recruitment of structures involved in visual processing, which support task performance through reliance on a visual strategy. It is also the case that the three tasks included in the Number comprehension domain, i.e., Number line marking, Number comparison, and Digit comprehension, all involve, to a large extent, visuo-spatial processing. As a consequence, when structures sup-porting this type of processes are subjected to a progressively volumetric loss, this is reflected by poorer performance on tasks which heavily rely on these areas.

No significant correlations between GM volume and arithmetical tasks were found in the group of control participants. Lack of sufficient variance in the scores of controls might explain this negative result. There is, however, some recently published evidence of significant associations between GM volume and measures of performance on number/arithmetic in the right interparietal sulcus, cuneus, and temporo parietal junction (Cappelletti et al., 2012). Based on this evidence it seems that numerical abilities in MCI patients are associated with regions that are not typically associated with numerical representations. It is therefore possible that, as shown for other cognitive abilities (Gardini et al., 2013; Rodríguez-Ferreiro et al., 2012), the anatomical associations detected with the VBM correlation models reflect progressive reliance over brain structures that are less affected by AD pathology which would take over in supporting performance over time. This spreading of associations may occur over several years as a compensatory and adaptive strategy to counteract the effects of AD neurodegeneration and sustain performance. This strategy, however, might be successful only for a while, but as pathology spreads, the cognitive sys-tem becomes progressively less and less effective. Regional associations become more loosely able to sustain behavioural performance, reflecting maladaptive rather than compensatory processes. The approach used in this study, however, cannot distinguish between compensatory and maladaptive spreading of significant associations. This kind of distinction can be achieved only by examining functional and structural connections between crucial regions normally associated with numerical and arithmetic processing. Future studies should focus on these parameters in this population of patients.

The association between volumetric variance and variability of performance on complex numerical tasks used in everyday life activities are harder to interpret. Money usage in the MCI group seems to recruit the temporal lobes bilaterally. Such tasks may rely on semantic information and, possibly, imagery. Moreover, Money-usage scores positively correlate with GM volume in the left mesial frontal cortex, right superior frontal cortex and right superior temporal areas in patients. Interestingly, significant positive correlations between Money-usage and WM volume were also found in the sub-lobar, extra nuclear area of the corpus callosum. Significant negative correlations were found between GM volume and the performance of control participants in ecological tasks. These negative correlations are likely to reflect the presence of more efficient structural networks that support performance (Grady, 2012). Thus, presumably, healthy participants who show lower levels of performance recruit larger and possibly less efficient networks, while high-performing controls recruit less widespread regions but have higher levels of computational optimization.

On the whole, these findings may reflect a deficit in processing that, in addition to other areas, involves the frontal lobes bilaterally in a task that requires coordination of disparate sources and an overload of attention where computational capacities begin to fail. This observation is in agreement with evidence found in several other studies. For instance, more intense reliance on frontal lobe activity is required in learning tasks that are unfamiliar, and when additional resources are needed to sustain the best possible level of performance in such challenging circumstances (for the anatomical correlates of math learning, see Delazer, Domahs, et al., 2003). However, MCI adults cannot rely on this compensatory mechanism endlessly, as their frontal lobes will ultimately end up being called into action and, then, fail.

Study 3: Numerical Activities of Daily Living in adults with Neurofibromatosis type 1

(Under review in Journal of Intellectual Disability Research)

3.1. INTRODUCTION

Neurofibromatosis type 1 (NF1) is one of the most common single-gene disorders leading to central nervous system abnormalities. Approximately one person in 3,500 is affected with NF1, which results from a mutation in the NF1 gene located on chromosome 17q11.2. The NF1 gene is involved in cell growth and differentiation, its mutation cause benign and malignant tumour growth and variable neuropsychological phenotypes across affected individuals.

NF1 mutations have been also associated with cognitive deficits, learning disabilities (Acosta, Gioia, & Silva, 2006; Hyman, Shores, & North, 2005; North, Hyman, & Barton, 2002) and mean lower IQ (Hyman et al., 2005). Specific cognitive impairments include deficits in expressive and receptive language skills (Levine et al., 2006), visuo-spatial and visuo-perceptual learning and memory (Varnhagen et al., 1988), executive functions, including significant working memory impairments, and difficulties with sustaining and switching of attention (Acosta et al., 2006).

Besides the various behavioural and cognitive problems associated with NF1, most children with NF1 display academic limitations. In particular, children with NF1 exhibit impairments in basic reading and reading comprehension tasks (Cutting, Koth, & Denckla, 2000; Levine et al., 2006). Moreover, there is a high incidence of mathematical learning disabilities among NF1 individuals, which appear dissociated from the incidence of reading deficits (Orraca-Castillo, Estévez-Pérez, & Reigosa-Crespo, 2014). A topic of current debate regards, in fact, the nature of the deficit in mathematical performance in NF1. A recent study showed that core numeric capacities (i.e. counting, number comparison, etc.) appear unaffected in this population, suggesting that they might not be responsible for the NF1 calculation dysfluency (Orraca-Castillo et al., 2014). Some authors have proposed that math difficulties in NF1 could be due to the general-domain cognitive deficits observed in this population (Moore, 2009), which should conceivably result in an overall deficit across different numerical tasks. Numerical difficulties in NF1, however, have been mostly identified using general performance tests, so it is difficult to discern which aspect of numerical cognition is actually compromised in this population. A few studies have reported specific deficits for instance in calculation (Cutting et al., 2000) or math word problems (Billingsley et al., 2004), but further studies failed to concur with these conclusion (Mazzocco, 2001). Crucially, no detailed description of the NF1 individuals' performance on separated operations (i.e. addition, subtraction, multiplication, etc.) has been reported so far in the literature. This opens the question of whether the heterogeneous patterns observed across the studies of mathematical cognition in NF1 are due to the different evaluation tests used and the relative weight each of them gives to different calculation exercises. A separate analysis of the calculation scores should contribute clarifying this issue and should also provide some insights into the source(s) of mathematics difficulty in NF1. The present study explores this issue in a group of adult individuals with NF1.

Neuropsychological and behavioural data in NF1 adults are less frequently reported than in children, and also more controversial. Riccardi & Eichner for instance reported IQ improvements as people with NF1 age (Riccardi & Eichner, 1986). However, Ferner et al. studied NF1 patients from 6 to 75 years of age and found no IQ discrepancy between children and adults with NF1, suggesting that IQ in NF1 patients remains low throughout development (Ferner, Hughes, & Weinman, 1996).

In the last decades, however, some efforts have been made to better understanding the cognitive profile of NF1 in adulthood. By comparing the neuropsychological profile of 30 NF1 adults to 30 controls, Zöller et al., found that adults with NF1 had problems in inductive reasoning, visual-constructive skills, visual and tactile memory, attention, logical abstraction, cognitive speed, coordination and mental flexibility (Zöller, Rembeck, & Bäckman, 1997). Interestingly and differently from what has been reported in children with NF1, basic motor speed and vocabulary were not impaired in the adult NF1 sample. Similar and more detailed results in NF1 adults have been reported in further studies addressing the NF1 adult patients' selective attention (Pavol et al., 2006; Uttner et al., 2003), auditory working memory, and long-term memory (Descheemaeker et al., 2013). A consistent finding in the literature regards the visual-constructive deficits in the NF1 group across the lifespan (Hyman et al., 2005; Zöller et al., 1997) and deficits in executive functioning (Hyman et al., 2005; Pavol et al., 2006; Uttner et al., 2003; Zöller et al., 1997).

Remarkably, even though individuals with NF1 tend to show substantial deficits in mathematics, more so than for reading and writing (Levine et al., 2006), the characterization of mathematical abilities in adults with NF1 and its impact on the patients' everyday life has received no attention in the literature. Number processing and calculation are an essential part of our culture, they considerably impact academic achievement, completion of higher education and career choice (Acosta et al., 2006) and significantly influence the independence and daily functioning of young and older individuals (Benavides-Varela et al., 2015; Benavides-Varela, Passarini, et al., 2016; Semenza et al., 2014).

The aim of this study was thus to contribute to filling this gap by investigating different aspects of formal numerical cognition in adult patients with NF1 and also their impact on daily living activities involving numerical aspects by means of the Numerical Activities of Daily Living (NADL) (Semenza et al., 2014). Given the numerical deficits characterizing the psychological profile in NF1 children, and the frequently reported continuum between childhood and adulthood in certain cognitive domains (Descheemaeker et al., 2013; Uttner et al., 2003), one can hypothesize that numerical deficits will be a common feature also among NF1 individuals in adulthood.

Functional and ecological measures, on the other hand, may not always be consistent with the neuropsychological profile in NF1, as shown by a previous study of Payne and colleagues which found attention and executive deficits in children with NF1, but no consistent relationships between the cognitive tests and the functional outcomes (Payne et al., 2011). No prediction is thus made as to whether the hypothesized deficits in mathematics would reflect a functional deficit in everyday numerical tasks. In order to provide a refined description of the numerical abilities in this population, scorings of the different calculation tasks will be analysed separately.

3.2. METHODS

3.2.1. PARTICIPANTS

Fifty-six adults [28 with NF1 (17 females, mean age 32.9 ± 11, education 12.4 ± 3.9) and 28 healthy controls (15 males, mean age 37.8 ± 9.6, education 12.8 ± 3.6)] were recruited from a specialist Clinic for patients with neurofibromatosis and genetic disorders (Clinical Genetics Unit, Department of Women's and Children's Health, Padova Hospital). NF1 participants fulfilled diagnostic criteria specified by the National Institutes of Health (1988) statement. Participants were excluded if any of the following criteria were met (1) under 18 years of age; (2) abnormal vision or hearing that could not be corrected to normal; (3) MMSE < 26; (4) history of psychiatric disorder, drugs or alcohol abuse; or (5) presence of a genetic or neurological condition (other than NF1 in the group of patients) that could affect test performance. There were no significant differences between the group of patients and the control group in age t(54) = -1.72, p = .09, scholastic attainment estimated in years of education t(54) = -.42, p = .67, gender t(54) = -1.06, p = .29, the Mini Mental State Examination scores t(54) = -1.48, p =.15, and scores on the instrumental activities of daily living (IADL) t(54) = -.60, p = .52. Written informed consent was obtained from all participants according to the Declaration of Helsinki and the study was approved by the Institutional Ethics Committee of the IRCCS San Camillo Hospital Foundation, Lido-Venice. Demographic and clinical data of all participants are reported in Supplementary Material 3. Written informed consent was obtained from all participants according to the Declaration of Helsinki and the study was approved by the Institutional Ethics Committee of the IRCCS San Camillo Hospital Foundation, Lido-Venice.

3.2.2. Measures

The ***Numerical Activities of Daily Living (NADL)*** standardized test was used to examine numerical abilities. This measure assesses both formal numerical abilities acquired during school years and the impact of numerical abilities on participants' everyday life (Semenza et al., 2014). Three subsections of the NADL were administered to the participants: A) A brief Interview which assesses the participant's awareness of possible difficulties in everyday life activities related with numbers (e.g., "Do you shop by yourself?"; "Do you make your own telephone calls unaided, do you dial them yourself?"); B) An Ecological performance test which measures the participants' competence in everyday numerical tasks (e.g. If a shirt normally costs €50, but is reduced by 10% how much will you have to pay for it?); C) A Formal Test of mathematics, assessing a wide range of numerical and math abilities (i.e. Number comprehension; Reading and Writing numbers; Mental Calculation; Rules and Principle comprehension; Written operations).

The ***Mini-Mental-State Examination (MMSE)*** was administered to all patients to exclude general cognitive impairment. Participants were also administered a measure of ***instrumental activities of daily living (IADL)***. This scale collects information concerning the person's ability to cope with everyday tasks: Food Preparation; House Keeping; Laundry; Mode of Transportation; Responsibility for own Medication; Ability to Handle Finances. The NADL and the neuropsychological tests were individually administered by a trained neuropsychologist in a single session lasting about two hours.

3.2.3. Data Analysis

Statistical analysis was conducted using Matlab R2009b. Assumptions of normality (Kolmogorov-Smirnov test) and homoscedasticity (Bartlett multiple-sample test) were tested. Significantly skewed data were compared using the non-parametric Wilcoxon rank sum test. Parametric data for patients and controls were compared with independent t-tests. One-tailed were used for the group NADL performance comparisons because a directional effect was hypothesized. Categorical data were compared with $\chi 2$ tests. Holm-Bonferroni correction was used for multiple comparisons.

3.3. Results

The scores of the patients and controls in each subsection of the NADL are shown in **Table 3.1**. The comparative analyses showed significant differences between the groups in specific tasks of written operations, logic and principles, and number comprehension domains of NADL (Formal Test). Specifically NF1 showed lower scores than controls in written subtractions $t(54) = -3.20$, $p < .005$, written multiplication $t(54) = -2.63$, $p < .01$, principles of multiplication $t(54) = -2.36$, $p < .05$, and digit comprehension (dot counting) tasks $t(54) = -2.29$, $p < .05$. No other tasks showed significant group differences (all *p*s > .05). Moreover no significant differences in the Interview and the Ecological numerical tasks were found between NF1 patients and controls.

3.4. Discussion

The aim of this study was to examine mathematical proficiency in adults with NF1 relating it with their ability to deal with activities of daily living involving numbers and calculation. The results showed that adults with NF1 had significantly lower scores than healthy controls even in simple dot counting tasks. This does not seem in line with previous studies showing that core numeric capacities (e.g. counting) are not affected in children with NF1 (Orraca-Castillo et al., 2014). It is however likely that NF1 patients applied the counting procedure correctly but, because of their visuo-spatial and visuo-perceptual limitations (Varnhagen et al., 1988), they failed to fully scan the visual display presented in this particular task. In fact, a close look to the errors in this task showed that the most of the mistakes were underestimations of the number of dots, confirming that the patients were unsuccessful in the visual search, possibly not in the counting per se.

Table 3.1 | Summary of behavioural results.

	Interview with patient (max. 10)
	Mean (SD)
NF	9.5 (0.84)
Healthy Controls	9.82 (0.39)

	Informal test of numerical abilities						
	Mean (SD)						
	Time estimation (max. 5)	**Measure (max. 1)**	**Transportation (max. 1)**	**Communication (max. 1)**	**Semantic knowledge of numerical information (max. 7)**	**Money usage (max. 8)**	**Total score (max. 23)**
NF	4.5 (0.7)	0.9 (0.1)	0.8 (0.4)	0.96 (0.1)	6.1 (0.7)	7.4 (0.7)	20.8 (1.9)
Healthy Controls	4.9 (0.2)	1.0 (0.0)	0.7 (0.5)	1.0 (0.0)	6.1 (0.8)	7.7 (0.6)	21.5 (1.2)

	Formal test of numerical abilities							
	Mean (SD)							
	Number comprehension (max. 19)	**Reading Arabic numerals (max.5)**	**Writing Arabic numeral (max. 5)**	**Mental Calculation (max. 18)**	**Knowledge of calculation rules (max. 7)**	**Logic and principles (max. 8)**	**Written Operations (max. 17)**	**Total score (max. 79)**
NF	16.7 (1.5)	4.7(0.5)	4.8 (0.3)	16.4 (2.0)	6.1 (1.0)	6.4 (1.3)	12.7 (2.1)	69.3 (6.4)
Healthy Controls	17.6(1.1)	4.8(0.5)	4.8 (0.4)	16.4 (1.9)	6.5 (0.7)	7.1 (1.1)	13.6 (1.6)	72.3 (4.4)

The results also evidenced NF1 patients' deficits in written calculation, in particular subtraction and multiplication, leaving the easiest task, i.e. addition, unaffected. This impairment might be due to a general reduction of cognitive resources, motor, or visuo-spatial impairments affecting the hardest tasks (Mazzocco, 2001; Moore, 2009). Unfortunately, we were unable to further assess specific cognitive functions besides the number domain, leaving unsolved the question of whether the observed pathological performance in NF1 should be considered a pure mathematical deficit, a more generic deficit or rather a consequence of other cognitive deficits frequently found in NF1. Correlating, for instance, the performance in numerical and neuropsychological tests of attention, working memory, executive functions, etc. should contribute to further clarify this issue.

For the time being, the results of our study show, for the first time, that numerical deficits previously identified in children with NF1 do not resolve with age. The findings also show that these deficits affect calculation but not the basic comprehension or representation of numbers. These data have important implications for designing cognitive interventions tailored to the cognitive profile of NF1 individuals.

Last but not least, our study shows that, NF1 deficits in calculations are somehow compensated when applied to more ecological situations. In fact, though NF1 adults failed school-like abstract subtractions and multiplications, they performed like healthy participants in tasks involving similar calculations but applied to money usage, time estimation, and other daily numerical activities.

3.5. Conclusion

The present study shows numerical deficits in adults with NF1, in particular written subtractions and written multiplications. No deficits in numerical ecological tasks were found suggesting the use of compensatory strategies on daily living activities involving numbers. This study offers new evidence to the neurocognitive phenotype of NF1, contributing to an in-depth understanding of this condition, but also to possible assessment and rehabilitation protocols for the cognitive deficits associated with NF1.

Study 4: Re-assessing acalculia: Distinguishing Spatial and purely Arithmetical deficits in right-hemisphere damaged patients

(Accepted in Cortex)

4.1. Introduction

Is there a calculation impairment typical of lesions to the right hemisphere? If so, to what extent such deficit should be considered secondary to non-numerical/spatial cognitive functions? For many years the notion of "spatial acalculia" was generally applied to any calculation deficit emerging after right-hemisphere brain lesions. However, a detailed description of the RHD patients' errors and its association with specific cognitive functions and brain regions was rarely attempted.

A number of studies investigated different aspects of number and calculation processing by focusing on lateralisation, i.e. whether they related to functions or lesions of one of the two hemispheres, and on the comparison between left brain damaged patients, right brain damaged patients, and a control group of healthy participants (Basso et al., 2000; Dahmen et al., 1982; Hécaen, 1962; Hécaen & Angelergues, 1961; Jackson & Warrington, 1986; Rosselli & Ardila, 1989). Most of these studies converged on the fact that patients with lesions to the left hemisphere have greater overall impairment than the right hemisphere lesion group and the controls. Importantly, they also reported that right-hemisphere damaged patients present deficits in specific numerical and calculation domains.

What is the primary cause of these numerical deficits? Since the earliest report from Henschen (1926), most studies seem just to have assumed that acalculia from a right-hemisphere lesion was secondary to spatial disorders or to a generalized reduction of cognitive resources (see, for reviews Hartje, 1987; Miceli & Capasso, 1999). Subsequently, in describing right hemisphere acalculia, some authors -almost accidentally- reported the presence of errors of non-spatial nature (Basso et al., 2000; Grafman, Passafiume, Faglioni, & Boller, 1982). While these authors acknowledged no correspondence between numerical and visuo-spatial deficits, they did not discuss the nature of such errors any further and did not venture in any theoretical interpretation about what the right hemisphere may do in calculation. A study by Ardila & Rosselli (1994) proposed for the first time that numerical deficits in RHD patients were due to proper numerical deficits (e.g. inability to evoke mathematical facts and remember their appropriate uses) however their conclusions were based on anecdotic descriptions: they did not include a control group and no statistical analyses were performed.

Recent studies, using different approaches have obtained similar conclusions, namely that the causal relation between visuo-spatial and numerical deficits might not be so straightforward. Granà and colleagues, for instance, reported the case of a patient who displayed difficulties in retaining the visuo-spatial layout necessary for dealing with multidigit multiplication. In particular, the patient, while knowing what, when, and how to carry out the various steps, did not know where to place the results of the intermediary and final steps of the calculation. Crucially, the pattern of errors could not be adduced to neglect deficits (Granà, Hofer, & Semenza, 2006).

In another study, a group of 24 RHD patients with and without unilateral left-neglect was examined in order to explore whether basic calculation and number processing would be affected by the presence of neglect. The results showed that measures of neglect did not relate with errors in mental calculation tasks, suggesting that visuo-spatial and arithmetical deficits are partially independent (Benavides-Varela et al., 2014). Still, the restricted number of items of the battery used in this study, which was appropriately designed for basic clinical screening, did not allow further correlations with specific error categories, and the relation between numerical impairment and other general-purpose cognitive processes was not explored.

Another study by Benavides-Varela and collaborators recently highlighted the role of the right hemisphere for transcoding complex digits, particularly those containing *zeros* (Benavides-Varela, Passarini, et al., 2016). The study showed that processing zeros requires specific mechanisms mainly grounded in the right insula and possibly also the right parieto-frontal connections. Lesions to these regions impaired the operation of overwriting *zeros*, which relies in turn on the capacity to merge the information derived from a previous intermediary process of transcoding (see Power & Dal Martello, 1990). Moreover, right hemisphere-damaged patients struggled with the transcoding of *zeros* in complex numbers due to their difficulties in setting-up appropriate empty-slot structures, and in the parsing and mastering of the categorical spatial relations between digits. These functions stand apart from other mechanisms necessary for completing transcoding tasks with other numbers, do not seem to be totally reduplicated in the left hemisphere (otherwise there would not be errors in such patients), and do not entirely depend on generic processing resources. Moreover, the investigation showed that the processes required for dealing with *zeros* do not relate to Neglect deficits.

Overall, these studies show that the right-hemisphere supports certain numerical abilities independently of other general-purpose mechanisms, which is in line with several studies using transcranial magnetic stimulation (Andres, Pelgrims, Michaux, Olivier, & Pesenti, 2011; Maurer et al., 2015; Salillas, Semenza, Basso, Vecchi, & Siegal, 2012), neuroimaging findings (Price, Mazzocco, & Ansari, 2013; Rosenberg-Lee, Chang, Young, Wu, & Menon, 2011), and intraoperative functional mapping of numerical functions (Della Puppa et al., 2013, 2015; Semenza, Salillas, De Pellegrin, & Della Puppa, 2016; Yu et al., 2011). In particular, a meta-analysis conducted on functional MRI-based studies (Arsalidou & Taylor, 2011) revealed a bilateral complex network supporting the resolution of numerical tasks. The study also found that neural activity is dominant in the right hemisphere for subtraction, and primarily in the right hemisphere for multiplication.

Although the role of the right hemisphere in numerical processes seems undeniable, the reason(s) why right hemisphere acalculic patients err the most, and, in particular, which features of their calculation deficit should be considered “spatial” or secondary to visuo-spatial functions is still unclear. The aim of the present study is, thus, to contribute filling this gap by assessing a group of RHD patients with focal lesions of various extents on a wide range of calculation and numerical tasks. This study also provides a first indication of the impact of numerical disorders on the RHD patients' everyday life.

4.2. MATERIALS AND METHODS

4.2.1. PARTICIPANTS

Thirty patients (17 males; mean age = 60.0 years, SD = 13.3; range: 29-85; mean education = 11.1 years, SD = 4.6; range: 5-23) who had suffered a right-hemisphere stroke participated in the study. Inclusion criteria were absence of dementia according to the NINCDS-ADRDA criteria (McKhann et al., 1984, 2011), substance abuse, psychiatric disorders, and vigilance impairments as diagnosed by a neurologist and a neuropsychologist. All patients were right-handed and had unilateral right-hemisphere lesions, as documented by MRI scans. Demographic and clinical data are reported in Supplementary Material 4.

A control group of 35 participants (N = 17 females; mean age = 60.0 years, SD = 12.19; range: 21-71; mean education = 10.9 years, SD = 4.56; range: 5-20) with no history of neurological or psychiatric illness and Mini-Mental State Examination scores > 26, was also tested. There were no significant differences between the group of patients and the control group in age $Z = -.28$, $p = .77$, scholastic attainment estimated in years of education $Z = -.00$, $p = .99$, or gender distribution $Z = -.41$, $p = .68$. The data of all participants were collected in accordance with the Helsinki Declaration II and the Institutional Ethics Committee of the IRCCS San Camillo Hospital Foundation, Lido-Venice, Italy.

4.2.2. NUMERICAL ASSESSMENT

All participants completed three sub-sections of the Numerical Activities of Daily Living test-NADL (Semenza et al., 2014). NADL measures the impact of specific numerical abilities on participants' everyday life, and has been successfully used to determine acalculia as well as the profile and the magnitude of numerical deficits in other clinical populations (Benavides-Varela et al., 2015). The sub-sections administered to the participants included:

- A brief **Interview** with the participant, which assesses the patient's awareness of their possible numerical deficits in everyday life.
- An **Informal** test of numerical competence that measures the participants' numerical proficiency in everyday tasks. It encompasses questions in the domains of Time, Measure, Transportation, Communication, General Knowledge, and Money.
- A **Formal** Test of Numerical Abilities, which assesses the patients' scholastic numerical abilities using brief sub-tests graded for difficulty. It assesses the domains of Number Comprehension, Transcoding, Mental Calculation, Rules and Properties of calculation, and Multi-digit Operations.

4.2.3. Quantitative Analysis of NADL scorings

The comparison between the performance of healthy control participants and patients was carried out using the non-parametric Wilcoxon rank sum test. This test was chosen because of the lack of homogeneity of variance between groups as measured with Bartlett multiple-sample test (NADL-1 $\chi^2(1) = 12.57$; $p < .005$; NADL-2 $\chi^2(1) = 11.03$; $p < .01$; NADL-3 $\chi^2(1) = 19.85$; $p < .0001$) and also because the data were not normally distributed (Kolmogorov-Smirnov test for NADL-1 $D = .44$, $p < .005$; NADL-2 $D = .40$, $p < .01$; NADL-3 $D = .40$, $p < .01$). In an initial analysis, the scores of the two groups in the three sub-sections of the NADL were compared, setting Bonferroni's correction for multiple comparisons (alpha = .01). In a second analysis, each domain of the Informal and Formal assessments was contrasted between groups, adjusting the significance level according to the number of comparisons carried out within each sub-section (alpha = .008).

4.2.4. *Quantitative coding*

The different types of errors identified in the patient's responses to the Formal assessment are listed in Supplementary Material 4. When appropriate, the errors were further classified as: 1) *Spatial*, namely those evidencing the misuse of spatial configurations in the visual input/ motor output of the tasks (e.g. omission of digits or dots, distortion of digit's shape, misalignment, etc.); and 2) *Numerical/arithmetical*, in which mathematical procedures failed (e.g. forgetting arithmetical facts, failing to apply the principles of additions and multiplication, failures to carry or to borrow, etc.). Furthermore, transcoding errors were classified according to the traditional lexical/syntactic distinction (McCloskey et al., 1985).

4.2.5. *Regression Analysis*

To determine the role of cognitive abilities underlying the errors committed by the group of patients, we performed separate stepwise regressions over the absolute frequency of *Spatial* and *Numerical/arithmetical* errors across tasks (separate analysis by task can be found in Supplementary Material 4). Composite measures were formed on the basis of previous theoretical indications of the cognitive domains associated to number cognition (Cappelletti, 2015) and also our hypothesis that output/input visuo-spatial functions may not explain the full range of deficits in this category of patients. Therefore, three composite measures, resulting from the averaged z-scores of the single neuropsychological tests, were included as predictors:

1) *Visuo-spatial attention/Neglect*: including both a Neglect assessment using the sum of specific subtests of the Behavioural Inattention Test part Conventional (BIT-C; Wilson, Cockburn, & Halligan, 1987), namely line crossing, letter cancellation, star cancellation, line bisection; and an *Attention* assesment by means of the digit cancellation test as in attentional matrices.

2) *Executive control/memory*: including neuropsychological measures of Executive functions (i.e. the phonemic verbal fluency test); Short term memory (i.e. digit span forward); and Working memory (i.e. digit span backward).
3) *Representational abilities*: including the sum of the patients' scores on figure and shape copying and representational drawing tests that assess the patients' abilities to draw objects based on imaginary representations. These tasks are normally part of the BIT-C, however, different from other tasks included in the battery, they are mostly sensitive to eventual deficits in representational abilities (Wilson et al., 1987), so they have been included as separate predictors in the regression analyses.

The use of composite scores allowed us to reduce sensibly the risk of multicollinearity and potential instability of single variables. The input data was scaled using z-scores to improve conditioning of the stepwise regression function in Matlab.

4.2.6. Voxel-based lesion–symptom mapping analysis

For all patients, CT, MRI T1 and/or T2-weighted scans were used to determine lesion location. Lesions were drawn on axial slices of a T1-weighted template using the MRIcron software package (Rorden & Brett, 2000). The lesion was mapped onto each single slice where the lesion was present (slice thickness = 1mm). An experienced neuroradiologist, who was blind to the purpose of the study, defined the lesion extensions. The voxel-based lesion–symptom mapping (VLSM) technique (Bates et al., 2003; Rorden, Karnath, & Bonilha, 2007) was implemented using the nonparametric mapping (NPM) software that is distributed as part of the MRIcron toolset. Specifically, the Brunner and Munzel test was applied to identify voxels that, when injured, predicted a greater number of errors in a specific NADL sub-test. To minimize possible outlier effects, the analyses were conducted only on voxels damaged in at least two patients. The resulting statistical map was adjusted for multiple comparisons by using False Discovery Rate correction $p < 0.05$.

4.3. RESULTS

4.3.1. NADL SCORINGS

The scores of the two groups in the three NADL sub-sections and corresponding domains are summarized in **Table 4.1**. The first set of analyses comparing the scores of the two groups in the three NADL sub-sections (total scores) showed significant differences between groups in the Interview (Z = -4.28, p < .0001), and the Informal (Z = -3.16, p < .001) and Formal assessments (Z = -2.22, p < .01). The subsequent set of analyses carried out on the domains of the Informal Numerical competence test showed that patients and controls significantly differed in General knowledge of numerical facts in everyday life (Z = -3.08, p < .005); there was also a tendency towards significance in Time estimation (Z = -2.43, p = .01) and Money usage (Z = -2.56, p = .01). The same set of analyses carried out in the domains of the Formal test showed significant differences between the groups in Number comprehension (Z = -3.02, p < .005), in which 37% of patients performed below the NADL cut-offs. A similar tendency was found in Transcoding (Z = -2.01, p = .04) with 27% of the sample performing below the cut-off, and Written operations (Z = -2.52, p = .01), in which 47% of the patients performed below the cut-offs. No other domain showed significant group differences (all ps > .05).

Table 4.1 | NADL scores of the patients and controls.

	Interview (max. 10)
	Median; range
Patients	9; 4-10
Healthy Controls	10; 6-10

	Informal test of numerical abilities						
	Median; range [below cut-off]						
	Time estimation (max. 5)	Measure (max. 1)	Transportation (max. 1)	Communication (max. 1)	General knowledge of numerical facts in everyday life (max. 7)	Money usage (max. 8)	Total score (max. 23)
Patients	4; 0-5	1; 0-1	1; 0-1	1; 0-1	5; 3-7	7; 3-8	18; 12-23 [14]
Healthy Controls	5; 4-5	1; 0-1	1; 0-1	1; 0-1	6; 4-7	8; 5-8	21; 18-23 [2]

	Formal test of numerical abilities					
	Median; range [below cut-off]					
	Number comprehension (max. 19)	Transcoding (max. 10)	Mental Calculation (max. 18)	Rules and Principles (max. 15)	Written Operations (max. 17)	Total score (max. 79)
Patients	16; 2-19 [11]	9; 7-10 [8]	17.5; 12-18 [3]	13; 5-15 [6]	12.5; 4-17 [14]	66.5; 38-79 [12]
Healthy Controls	17; 15-19 [1]	10; 8-10 [0]	17; 14-18 [2]	12; 8-15 [3]	14; 11-17 [1]	70; 59-77 [0]

4.3.2. QUALITATIVE ANALYSIS OF ERRORS

Table 4.2 reports the type and frequency of errors made by the patients in the different domains of the Formal Assessment. As expected, omission of elements in the left hemi-space was very frequent in the Dot Comparison and Dot Counting tasks; deviations to the left or the right side from the target point were equally frequent in the Number Line test (p = .79). Regarding transcoding, we found that the number of lexical and syntactic errors were comparable in both the reading (p >.05) and writing tasks (p >.05). Moreover, a close examination of the errors showed that 94% and 76% of the syntactic and lexical errors respectively were found in numbers containing the digit *zero*. In mental calculation, in particular mental subtractions, basic fact errors (i.e. forgetting arithmetic facts) were the most common (54.5%). Operand errors were the most common ones in the mental multiplication task, adding up to about 43%. Moreover, in accordance with previous reports in the neuropsychological literature (McCloskey, Harley, & Sokol, 1991), Operand errors that correspond to the preceding/following problem in the times-table (i.e. Operand errors close) were more common than errors including distant Operands (i.e. Operand errors far). For Rules and Principles and Written calculations we generally found a greater number of *Numerical/arithmetical* errors than *spatial* ones (over 74% of the errors were *Numerical* in all the tasks).

Finally, basic fact errors were the most frequent when patients carried out written additions (36%); they were also among the most common errors in written subtractions (25%), along with the Subtraction inversion (25%), and borrowing failures (21%). In the written multiplication task, there were various errors including irregular alignment of digits (10%), rule errors when multiplying by *zero* (9%), incomplete multiplication procedures (about 7%), Operand errors (about 9%) among others (see Supplementary Material 4 showing the full description of the error categories and their frequencies).

Table 4.2 | Absolute and relative frequency of the error categories by task.

Task	Type of error	Absolute and Relative frequency (%)	Number of patients
Number Comprehension			
Dots Comparison	Intrusions	1 (10%)	1
	Omissions	9 (90%)	6
Number Line	Leftward deviations	84 (49.7%)	25
	Rightward deviations	85 (50.3%)	25
Dot Counting	Dot intrusions	9 (17.6%)	6
	Dot omissions	42 (82.3%)	12
Transcoding			
Reading	Lexical	8 (44.4%)	8
	Syntactic	11 (55.5%)	7
Writing	Lexical	9 (56.2%)	9
	Syntactic	7 (43.7%)	6
Mental Calculation			
Mental Addition	Numerical/arithmetical	2 (100%)	2
	Spatial	0	0
Mental Subtraction	Numerical/arithmetical	10 (90.9%)	6
	Spatial	0	0
	No answer	1 (9.09%)	1
Mental Multiplication	Numerical/arithmetical	21 (75.0%)	12
	Spatial	0	0
	No answer	7 (25.0%)	3
Rules and Properties			
Principles of operations with zero and one	Numerical/arithmetical	29 (96.6%)	16
	Spatial	0	
	No answer	1 (3.3%)	1
Properties of Addition	Numerical/arithmetical	22 (74.19%)	13
	Spatial	3 (9.68%)	2
	No answer	5 (16.13%)	4
Properties of Multiplication	Numerical/arithmetical	24 (80.42%)	16
	Spatial	0	
	Random responses	2 (6.45%)	1
	No answer	5 (16.13%)	2
Written Calculation			
Additions	Numerical/arithmetical	26 (59.09%)	14
	Spatial	11 (25%)	6
	Random responses	7 (15.91%)	7
Subtractions	Numerical/arithmetical	52 (77.61%)	19
	Spatial	7 (10.45%)	6
	Random responses	6 (8.96%)	5
	No answer	2 (2.99%)	1
Multiplications	Numerical/arithmetical	46 (51.69%)	16
	Spatial	18 (20.22%)	12
	Random responses	16 (17.98%)	16
	No answer	9 (10.11%)	4

The last column indicates the number of patients committing each specific error.

4.3.3. COGNITIVE PREDICTORS OF NUMERICAL ERRORS

The regression analyses carried out over the general error classification across tasks are outlined in **Table 4.3**. The *Visuo-spatial Attention/Neglect* composite variable predicted the patient's overall frequency of Spatial (β = -3.18; $p < .0005$) and Syntactical errors (β = -.51; $p < .001$; Model $R^2 = .43$, $F(2, 26) = 21.16$; $p < .001$). *Representational abilities* predicted overall Numerical/arithmetical errors (β = -2.73; $p < .05$; Model $R^2 = .18$, $F(2, 26) = 6.54$; $p < .05$), and Spatial ones (β = -2.43; $p < .005$; Final Model $R^2 = .70$, $F(2, 26) = 32.17$; $p < .0001$). Results of the regressions analysis carried out for each task separately can be found in the Supplementary Material 4.

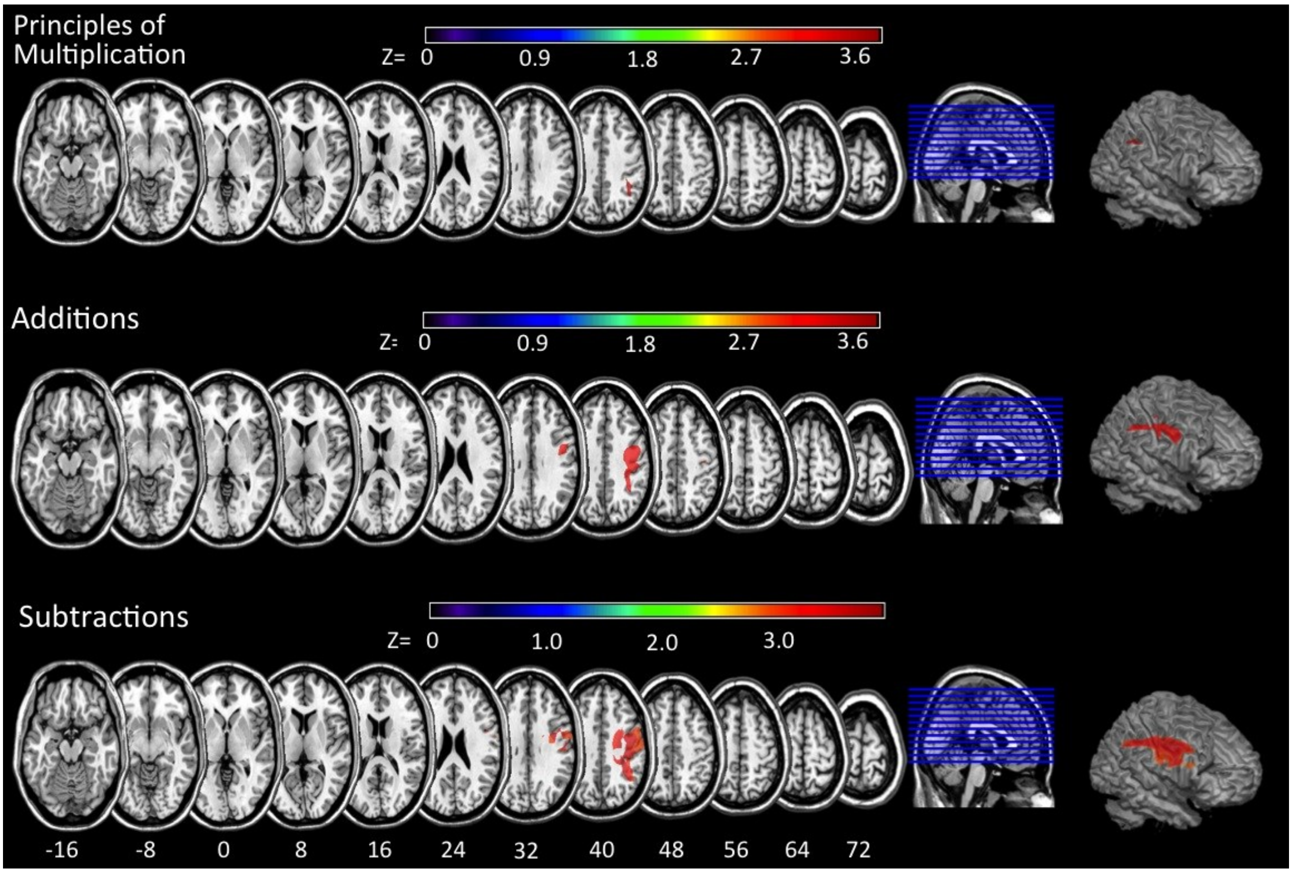
Table 4.3 | General error classification and corresponding measures predicting the errors in RHD patients.

General error classification	Cognitive Predictors
Spatial	– Visuo-Spatial Attention/Neglect – Representational Abilities
Numerical/arithmetical	– Representational Abilities
Lexical	—
Syntactical	– Visuo-Spatial Attention/Neglect

4.3.4. BRAIN LESIONS SIGNIFICANTLY ASSOCIATED WITH SPECIFIC TESTS

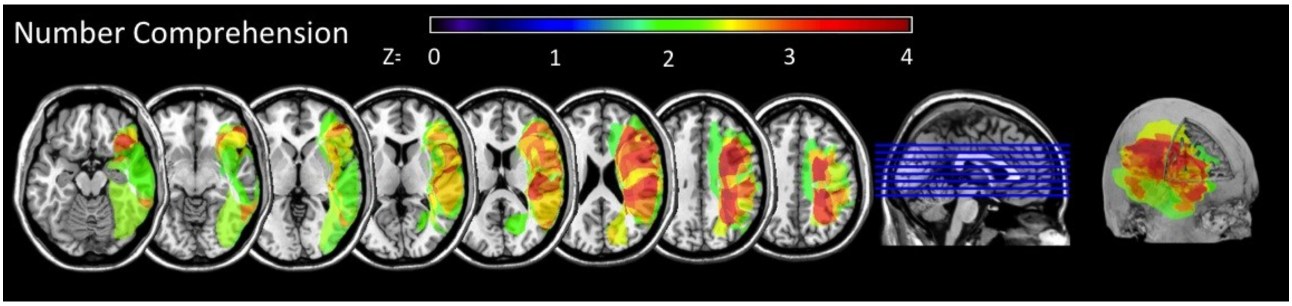
The findings indicated that patients' limited abilities to deal with principles of multiplication was associated with lesions to the right inferior-parietal areas in the proximity to the angular gyrus; lesions including the angular gyrus and extending more anteriorly were also associated with greater errors in addition and subtractions (**Figure 4.1**). Moreover, deficits in the Number Comprehension scale of the NADL battery were most frequently associated with extensive lesions in fronto-temporo-parietal regions frequently compromised in neglect patients (**Figure 4.2**). No other areas were associated with the performance of the patients in the subtests of the Formal or Informal assessments.

Figure 4.1 | VLSM for calculation tasks.



Statistical VLSM analysis showing the brain regions that, when injured, predicted a greater number of errors in calculation tasks. Separate results are shown for each error type. Presented are all voxels that exceed a corrected P < 0.05. MNI coordinates of each transverse section are given.

Figure 4.2 | VLSM for Number Comprehension.



Statistical VLSM analysis showing the brain regions that, when injured, predicted a greater number of errors in the Number Comprehension domain of the NADL. Separate results are shown for each error type. Presented are all voxels that exceed a corrected P < 0.05. MNI coordinates of each transverse section are given.

4.4. DISCUSSION

The current results showed that, contrary to what emerged from the traditional literature, RHD patients commit significantly more *Numerical/arithmetical* errors (e.g. failure to recall basic number facts, to carry, to borrow, etc.) than *Spatial* ones (e.g. omissions of the left-most digits related to visual neglect, misalignment, number inversions, etc.).

Such deficit in calculations and its association with specific lesions in the right parietal regions is in agreement with previous neuropsychological studies using other numerical batteries (Benavides-Varela et al., 2014; Granà, Lochy, Girelli, Seron, & Semenza, 2003), neuroimaging findings (Arsalidou & Taylor, 2011; Price et al., 2013; Rosenberg-Lee et al., 2011) (Andres et al., 2011; Cohen Kadosh et al., 2007; Göbel, Walsh, & Rushworth, 2001; Salillas & Semenza, 2014; Salillas et al., 2012), and intra-operative cortical electro-stimulation reports (Della Puppa et al., 2013; Semenza et al., 2016; Yu et al., 2011). The available data suggest, altogether, that lesions including the right angular gyrus and its proximity could be a possible cause of calculation deficits in RHD patients.

These observations suggested that the right hemisphere plays an essential role, complementary to that of the left hemisphere. While in fact the left hemisphere is crucial for the retrieval of verbally trained solutions from a stored repertory (Dehaene, Piazza, Pinel, & Cohen, 2003), the right hemisphere would contribute to the choice of the right solution by indicating the approximate solution (Semenza et al., 2016). Notice that previous studies uncovered the role of the right angular gyrus when participants solved basic arithmetic facts i.e. multiplication tables. Our study shows for the first time, the involvement of the right angular gyrus for successfully solving numerical problems that also involve multiplications but that cannot be solved on the basis of mere verbally trained solutions (e.g. if $94 \times 5 = 470$ then $93 \times 5 = ?$ where the subject is requested not to perform the full calculation, but to infer it from the premise).

Crucially, similar problems on additions (e.g. if $60 + 29 = 89$ then $61 + 29 = ?$) do not appear linked to this circumscribed region of the brain. A partial explanation for these findings can be derived from the regression analysis showing that tasks involving principles of multiplication were mostly supported by representational abilities whereas tasks involving principles of additions seemed more affected by attentional and neglect deficits. It is thus possible that the manipulation of quantities in the two types of calculations require different levels of abstraction/internal representation of information. However, further studies are necessary to draw firm conclusions on this respect.

Most calculation errors were non-spatial in nature and were predicted by measures of representational abilities. The failures at dealing with imaginary representations could affect various stages of calculation, for instance the ability to recall where to place the carried-over or borrowed quantity or internally keeping information about the order of items. Problems in applying general basic number facts (e.g. 2 + 3 = 4) were also obvious across calculation tasks, and could probably be associated with failures to make use of automatic procedures (Salillas & Semenza, 2014; Salillas et al., 2012) and employing strategies to scan possible answers (De Hevia, Vallar, & Girelli, 2008).

Patients showing more errors in the domain of Number Comprehension (which includes dots comparison, dot counting, and number line tasks in the NADL battery) showed completely different lesions and neuropsychological profiles as compared to the patients erring in the calculation domain. The lesions varied in extent and location among individuals and included the neural structures damaged more often in patients with spatial neglect, namely the right superior temporal cortex, the insula and subcortically putamen, and caudate nucleus(Karnath, Berger, Küker, & Rorden, 2004) (see also Heilman, Watson, Valenstein, & Damasio, 1983; for a differnt localization of the neglect deficits Vallar & Perani, 1986). Consistently, the errors in this domain were fundamentally of spatial nature and were predicted by measures of visuo-spatial attention/neglect. Therefore, these errors might be due to the impossibility of processing the left-hemispace, or because of visuo-spatial inattention (Holmes, 1918; Warrington & James, 1967), which manifests, for instance, in omissions and overestimation of dots present in the input space and significant deviations in the number line estimation. Visuo-spatial inattention and Neglect deficits are thus a confounding factor that should be carefully considered when deriving conclusions on the patients' proper numerical comprehension. Our results indicate that when a patient is affected by neglect, he/she will show a limited performance on the tasks included in the "Number comprehension" domain regardless of whether the patient has an additional problem in understanding magnitudes, estimating or comparing numerosities. Future studies assessing pure number comprehension abilities in this type of patients should thus attempt to minimize the effects of neglect by developing different methodologies of assessment. Presenting stimuli in vertical arrays, verbally, or in the right-hemispace only could be some of the possibilities that can be implemented according to each patient's specific clinical neglect subtype.

Because some errors were not predicted by the patients' scorings in the neuropsychological tests or associated with particular lesion patterns, no clear conclusions can be drawing regarding their origins in right-hemisphere damaged patients. It is unlikely, though, that the emergence of these errors among our patients reflected a breakdown of the same functions affecting numerical performance on left-hemisphere damaged patients. Let us consider the example of Operand errors, and in particular the Operand distance effect that is frequently found among healthy individuals (Campbell & Graham, 1985), left-hemisphere damaged patients (Sokol, McCloskey, Cohen, & Aliminosa, 1991) and that was also observed in our sample of RHD patients. In particular it is observed that mistakes with the preceding/following operand in the times-table e.g. $9 \times 7 = 72$ are more common than erroneous answers using a distant operand e.g. $9 \times 7 = 27$. A number of models (e.g., Ashcraft & Battaglia, 1978; Campbell & Graham, 1985; Siegler, 1988) have been proposed in the literature attempting to explain why such effect occurs. Crucially, none of these models were developed to account for the pattern of errors observed in neuropsychological patients. The most significant attempt to link each model to the patterns of impairment observed in patients (McCloskey et al., 1991) focused on a study including only left-hemisphere damaged patients (Sokol et al., 1991). Thus generally, the different explanations of why such errors occur converge so far to defective verbal associations between problems and (wrong) results. The fact that the same effect was observed in our sample suggests, however, that this pattern could also arise after the disruption of a different mechanism: faulty approximation (Semenza et al., 2016), magnitude estimation, or error-detection strategies in right hemisphere damaged patients. The actual origins of such type of errors in right hemisphere damaged patients will need to be tested in future research manipulating and providing different strategies while patients perform the tests.

Finally, the current study showed that numerical deficits in people with right-hemisphere lesions also impact some activities of daily living, in particular, time estimation, money usage, and retrieving general knowledge of numerical information. These findings should contribute to better defining the clinical profile of the patients, their independence, and daily functioning. Such information will also be crucial for building up appropriate rehabilitation programs that directly impact ecological activities of the patients.

4.5. Conclusion

Right-hemisphere acalculia is characterized by the presence of spatial as much as errors of numerical/arithmetical nature. Crucially, the distortion causing calculation problems is not confined to the left side of the mental outlines but interferes with the representation of numbers in diverse positions and at different stages of the arithmetic procedures. Many numerical errors are linked to non-spatial representational processing, and appear after lesions to the right angular gyrus and its proximity. Spatial errors are primarily associated to neglect and corresponding brain areas and mainly affect the execution of dots comparison, dot counting, and number line tasks (within the Number Comprehension domain of the NADL battery). Further research may want to compare the distribution of errors in right hemisphere acalculia with that found in left hemisphere acalculia. It is not clear how this comparison could be meaningful, however. One would expect, for instance, that errors in left hemisphere acalculia would be heavily determined by linguistic factors. Moreover, it is clear that errors determined by right hemisphere lesions cannot have exactly the same origin of errors following left hemisphere lesions. The right hemisphere does not reduplicate, in calculation, left hemisphere functions, otherwise a lesion would not provoke the deficits we observed here. It rather seems to play a distinctive, ancillary, role that goes much beyond spatial processing.

It is concluded that the concept of spatial acalculia should be distinctively used and clearly distinguished within the more general concept of right hemisphere acalculia.

Study 5: Numerical Activities and Information Learned at Home Link to the Exact Numeracy Skills in 5–6 Years-Old Children

(Published in Frontiers in Aging Neuroscience, 2016, Vol. 7)

5.1. Introduction

At the time children enter school education they already show great individual differences in their numerical performance (e.g., Aunola, Leskinen, Lerkkanen, & Nurmi, 2004). There are three reasons why this may be so. First, general cognitive factors, such as intelligence, working memory capacity, and so on, could differentiate individual learners (e.g., Bull, Espy, & Wiebe, 2008; Espy et al., 2004; Gathercole, Pickering, Knight, & Stegmann, 2004; Geary, 2011; Kroesbergen, Van Luit, Van Lieshout, Van Loosbroek, & Van de Rijt, 2009; Passolunghi & Lanfranchi, 2012; Passolunghi, Mammarella, & Altoe, 2008). Second, cognitive factors specific to the domain of numbers could be critical (e.g., Aunola et al., 2004; Booth & Siegler, 2006; Butterworth, 2010; Halberda, Mazzocco, & Feigenson, 2008; Reeve, Reynolds, Humberstone, & Butterworth, 2012; Siegler & Booth, 2004). Third, contextual factors, such as social, economic, parental influences, could play the key role. Of course, all these factors interact and it is difficult to determine their influence separately or indeed together (Butterworth, 2005). Here we focus on one contextual factor, numerical activities and knowledge acquired in the learner's home. In particular, we seek to assess the effects of numerical activities and the information learned within the family environment on two potential types of domain-specific capacities that we inherit: the Approximate Number System (e.g., Carey, 2004, 2009; Feigenson, Dehaene, & Spelke, 2004) and the Exact Number System (e.g., Butterworth, 2010; Gelman & Gallistel, 1986).

Parents usually report using literacy activities (e.g., sharing book reading) more frequently than numeracy activities with their children at home (Blevins-Knabe, Austin, Musun, Eddy, & Jones, 2000; Cannon & Ginsburg, 2008; LeFevre et al., 2009). The implementation of reading-related practices in family settings has been reinforced in the last decades by strong recommendations conveyed through the media and schools, which in turn rely on the findings of numerous studies on home literacy and the acquisition of reading skills (see Fletcher & Reese, 2005 for review). Similar contributions for promoting numerical practices at home are just being explored (Berkowitz et al., 2015), which call for further studies aiming at understanding how mathematical knowledge can be acquired outside of school.

5.1.1. Contextual Factors Influencing Arithmetical Attainment

Parents' expectations about numeracy play a significant role in the basic calculation skills of their children. One longitudinal study showed that children's attitudes toward mathematics were influenced more by their parents' beliefs about their child's abilities than by the child's own results in previous mathematical assessments (J. E. Parsons, Adler, & Kaczula, 1982). Sheldon and Epstein (2005) showed that parents who implemented specific practices to support math learning at home (e.g., discussing the student's homework, lending library activities, or playing games by indication of the experimenters) contributed to increasing the children's scores on math achievement tests. Kleemans et al. (2012) found similar results: the higher the parents' numeracy expectations, the better the child's early numeracy skills.

The socioeconomic background of the family also influences arithmetical development (Melhuish et al., 2008). A series of studies by Jordan a collaborators show that children from impoverished backgrounds display poorer numerical capacities than peers from advantaged backgrounds in tasks such as counting, adding, subtracting, and comparing magnitudes (Jordan, Kaplan, Nabors Oláh, & Locuniak, 2006; Jordan, Levine, & Huttenlocher, 1994). Similar conclusions were reached in a cross-cultural study derived from the Program for International Student Assessment–PISA—(Ming Chiu & Xihua, 2008). In the study, the authors evaluated the mathematical performance of more than one hundred thousand children from 41 countries and explored whether their scores related to characteristics of the family of origin. Consistent with previous evidence, it was reported that children who scored highest in the tests came from families that had more cultural possessions and higher socio-economic status.

5.1.2. The Influence of Home Numeracy Learning Experiences

One potential causal factor in the above studies is that socially more advantaged parents with higher numeracy expectations engaged in more numeracy-related practices, which in turn is associated with children's higher mathematics achievements (LeFevre, Polyzoi, Skwarchuk, Fast, & Sowinski, 2010). The pioneer study of Blevins-Knabe and Musun-Miller (1996) investigated the frequency of specific child and parent-child activities at home that directly involved the use of numbers. The results showed a positive correlation between activities that reflect direct number instruction (i.e., does the child say the words "one," "two," "three," or does the child mention number facts such as 1 + 1 = 2) and children's total scores on the standardized test of Early Mathematics Ability-Second Edition (TEMA-2 of Ginsburg & Baroody, 1990). Similarly, Huntsinger et al. (2000) found a positive correlation between the parents' deliberate efforts to teach their children simple sums and the children's later achievement in basic calculation skills. Moreover, LeFevre and colleagues found that the frequency of parent–child number teaching activities (i.e., counting, simple addition) was directly related to the counting abilities of their children (LeFevre, Clarke, & Stringer, 2002). Analogous results were found for Chinese speaking children: the frequency of parent–child numeracy activities was significantly related to later performance on counting and addition (Pan, Gauvain, Liu, & Cheng, 2006).

The above studies consistently show a relation between direct numerical instruction at home and children's math performance. With respect to the relations between numeracy knowledge and other daily activities that indirectly facilitate acquisition, the literature is much less developed. LeFevre et al. (2009) first proposed the distinction between direct and indirect numerical activities within the family environment. Direct activities are those typically used by parents for the explicit purpose of developing quantitative skills (e.g., counting objects, practicing number names, printing numbers).

In contrast, indirect activities are real-world tasks (e.g., playing card or board games) for which the acquisition of numeracy is likely to be incidental. The crucial distinction is that, although instruction in numeracy occurs in both types of activities, teachings are embedded in everyday tasks only in indirect numerical activities. In adults, recent studies have shown that formal mathematical performance and the use of numerical information in everyday activities might dissociate both at the behavioural (Semenza et al., 2014) and the neural level (Benavides-Varela et al., 2015). In children, to the best of our knowledge, only one study has been conducted so far showing how indirect experiences at home relate to children's quantitative skills. In particular, LeFevre et al. (2009) evaluated the relation between the frequency of home numeracy activities and children's performance on three subtests of the KeyMath test: addition, subtraction and numeration. The authors found a positive correlation between children's performance on the KeyMath and their frequency of participation in board games. Interestingly, the accuracy and latency of the children's responses also correlated with the frequency with which the parents reported using the calendars and dates, and talking about money within the family environment. Unfortunately this study, like previous ones, based its conclusions on single scores of performance tests (e.g., KABC battery in Anders et al., 2012; TEMA-2 in Blevins-Knabe & Musun-Miller, 1996) thus leaving unresolved the question of whether the activities within the family environment differentially affect specific mathematical skills and critically whether those skills rely on either the exact number system, or the approximate numerical system, or both. In agreement with the study of LeFevre and colleagues, Ramani and Siegler (2008) showed that playing linear number board games at home influences numerical knowledge in early childhood. However, instead of interviewing parents, the authors asked the children about the frequency and number of board games, card games, and videogames they played outside the school. The authors found a positive correlation between the amount of board game experience and the performance on four numerical tasks: numerical magnitude comparison, number line estimation, counting, and numeral identification. This study suggests that playing linear board games enhances the performance on tasks relying on both exact and approximate representations. However, this result was found only in a portion of the population under study whereas for the remaining kids, namely those from high socio-economical status, the association between performance on the tests and the frequency of playing board games was not found. Moreover, this study focused only on a single activity. It is thus unclear whether other activities within the family environment influence numerical understanding and to what extent they differentially impact exact and approximate systems.

5.1.3. The Present Study

Whilst the ability to roughly approximate the numerosities of sets is present in humans even from birth (Izard, Sann, Spelke, & Streri, 2009), the exact representation of numbers appears to develop later in life either by "bootstrapping" approximate into exact representations (Carey, 2004, 2009) or independently by mapping onto number words in the process of learning to count (Gelman & Gallistel, 1986; Leslie, Gelman, & Gallistel, 2008). It has been observed that formal education enhances the acuity of the exact, as well as the approximate representations (Piazza, Pica, Izard, Spelke, & Dehaene, 2013); and crucially that young children's skills on both approximate (e.g., Booth & Siegler, 2008; De Smedt, Verschaffel, & Ghesquière, 2009; Desoete, Ceulemans, De Weerdt, & Pieters, 2012; Mazzocco, Feigenson, & Halberda, 2011) and exact representations (e.g., Aunola et al., 2004; Geary, Bow-Thomas, & Yao, 1992; Passolunghi, Vercelloni, & Schadee, 2007; Reeve et al., 2012) are excellent long term predictors of later school mathematical performance. However, it is currently unknown to what extent the exact and approximate skills are also influenced by the activities and the numerical knowledge acquired in the household environment. Because home experiences often directly or indirectly imply sequencing and naming numbers (LeFevre et al., 2009), they are likely to influence tasks that rely on exact number knowledge. However, it is also possible that numerical activities within the family environment and knowledge acquire at home impact tasks relying on approximate representations, either by directly triggering changes in those representations (Ramani & Siegler, 2008) or through a connection between the exact and approximate systems. The last possibility gets support by work showing that children who know more number words and Arabic numbers also perform better in tasks relying on approximate representations (Mussolin, Nys, Leybaert, & Content, 2012).

In the present work, we thus aimed at studying the effects of indirect numerical exposure further, focusing on how activities within the family environment and the numerical information learned at home relate to each of the representational systems underlying mathematical performance. This information should contribute to understand the permeability of the exact and the approximate systems in early childhood and should consequently be useful to elaborate refined educational programs adapted to the needs of the learners who begin the transition from the family to the pre-school/school learning environments. The tasks implemented in the current study are well known in the field. They were adopted from established groups that have evaluated approximate representations in magnitude comparison (Halberda et al., 2008) and the number line tasks (Siegler & Booth, 2004); and exact representations such as counting (Geary et al., 1992) and one-to-one correspondence (van Luit, van de Rijt, & Pennings, 1994).

The current work is different from the previous studies in several respects. First and foremost: the abilities under investigation. The most influential study that has so far focused on the effects of indirect exposure to numbers in the family environment measured arithmetical performance (LeFevre et al., 2009). Our study additionally incorporates tests of approximate representations and crucially also of numerical problems in everyday situations. We reasoned that evaluating abstract arithmetic abilities (e.g., 1 + 3 = ?) in young children might provide an incomplete measure of their early mathematical intuitions because children are generally unfamiliar with the formal terms “plus,” “minus,” or “equals” before entering school. Measuring the same abilities applied to everyday situations (e.g., if you have one banana and I give you three more, then how many bananas do you have now?) should provide a clearer view of the children arithmetic intuitions and the way they interact with the numerical exposure received at home. Moreover, the present study incorporates a direct measure of the child knowledge of number facts that are learned through parental or familiar instruction (e.g., birthdates, phone numbers, etc.). Previous studies based their conclusions on parents' reports of family activities and not on the actual knowledge of the child.

The current measure, which we call "numerical information learned at home" directly inquires children numerical facts that are acquired within the family. It should therefore provide a closer approximation to the actual opportunities children have to learn this information. Finally, our study differs from previous ones in the sources of information regarding the specific activities and the frequency of those activities within the family environment. Specifically, while previous studies focused either on parental report (LeFevre et al., 2009; J. E. Parsons et al., 1982; Sheldon & Epstein, 2005), or an interview for children (Ramani & Siegler, 2008), the present study integrates these two approaches. Children accounts have the advantage of capturing information that parents may overrate or miss (Tudge & Doucet, 2004). Parental accounts, on the other hand, are more stable and less influenced by preferences or recent memories. Therefore, combining the information provided by parents and children and evaluating the consistency between them should offer a more reliable account than the one provided by each of these informants separately.

5.2. Methods

5.2.1. Participants

A hundred and ten pre-school children (59 females; 100 right-handers; mean age: 5.95 years-old; age range: 5.46–6.43 years-old) participated in the study. Participants were enrolled in the last year of kindergarten in five different urban and extra-urban schools of the province of Padua, Italy. The schools and teachers involved in the research were contacted in a meeting of Educational Psychology organized by the University. All children had normal or corrected-to-normal eyesight and their parents reported no history of health problems during pregnancy, infancy, or childhood that would compromise their perceptual or intellectual abilities. Direct measures of intellectual abilities were not obtained because the Italian policies allow them only for clinical purposes. The range of socio-economic status (SES) of the families was very wide as indexed by parental education and occupation. Parental education was coded on a six-point scale based on the level of education completed by each parent; zero = no schooling; one = primary school; two = middle-school; three = high-school or professional school; four = university degree; five = post-graduate studies. Occupation was coded on a scale of zero to two; zero = no occupation or not paid job; one = manual work; two = service sector or intellectual work. The level of education and occupation of the mother and the father were added into a single index of SES that ranged from 0 to 14. Families distributed according to the SES index in the following way: 1% were of high SES, 97.2% of middle SES, 1.8% of low SES. All parents provided informed consent for the tests and interviews. The data of all participants were collected in accordance with the Helsinki Declaration II and the Institutional Ethics Committee of the Psychology Department at Padova University.

5.2.2. General Procedure

Children completed a battery of numerical tasks, including tasks relying on approximate representations: magnitude comparison (Halberda et al., 2008) and number line task (Siegler & Booth, 2004); tasks relying on exact representations: counting (Geary et al., 1992), one-to-one correspondence (van Luit et al., 1994); and a task assessing children’s ability to solve math problems in everyday situations. Moreover an assessment of verbal short-term memory (digit span) was used as a covariate. All the tests were administered individually in a quiet classroom during school hours. A brief description of each of these tasks is presented in the following section.

Additionally, we obtained data about family activities from two questionnaires -one for the child and one for the parents. The child’s questionnaire (see Supplementary Material 5) was designed to directly assess the children’s knowledge of numerical facts acquired in the family environment such as birthdates, number of siblings, phone numbers. Each correct response scored one point. The total scoring of the children’s questionnaire corresponds hereafter to “numerical information learned at home.”

In order to assess congruency between parents' and children' s accounts of the information children knew, we also interviewed the parents about number-related information, asking whether they thought their children knew this information. Each affirmative response scored one point. We also asked parents about the family constitution and background. Moreover, parents indicated the frequency on a weekly basis of number-related and non-related activities of the child (e.g., playing board games, videogames, etc.) and those involving the family (e.g., shopping, reading, tv watching, etc.). A five-point incremental scale was used for scoring frequency: does not carry out this activity, does it for about 1, 2, 3, 4h, or more per week.

The criteria for including specific daily activities in the questionnaire derives from studies indicating that such activities facilitate academic performance and cognitive control more generally (e.g., playing videogames –Dye & Bavelier, 2004; reading –LeFevre et al., 2009; practicing sports –Trudeau & Shephard, 2008), or directly enhance numerical performance (e.g., frequency of shopping and talking about money with children –LeFevre et al., 2009; playing board games –Ramani & Siegler, 2008; Siegler & Ramani, 2008; music –Spelke, 2008). The activities chosen also corresponded to the most frequent activities typically occurring in Italian families (not necessarily benefiting scholastic performance, such TV watching –Christakis, 2009), and activities mentioned in similar research (A. G. Anderson, 1998; Blevins-Knabe et al., 2000; LeFevre et al., 2009). Cronbach's alphas for the questionnaire applied to children and parents were 61 and 68, respectively. These values are fully comparable with measures of internal consistency found in previous research on numbers in everyday activities (Semenza et al., 2014). Agreement between parents' answers and children's actual knowledge was on average 75.11%, *SD* = 15.68.

5.2.3. Numerical Tasks

The tests were administered individually in a silent room. No feedback was given, only general praise and encouragement. A brief description of each test follows.

- Counting tests assessed the child's mastery of the number word. The children were requested to count forwards (from 1 to 10; from 4 to 10) and backwards (from 6 to 1; from 10 to 1). Children were instructed to count as fast as possible. One point was given for each correct sequence.
- One-to-one correspondence task was adapted from the Early Numeracy Test (ENT-part A, van Luit et al., 1994). The task was composed of 5 tests designed to assess the children's ability to understand one-one relations between objects and numbers. For example, the child has 15 blocks and the experimenter shows a drawing representing two dice with 5 and 6. Then the experimenter asks: Can you put as many blocks on the table as are shown on the dice here? Each correct response scored one point.
- Magnitude comparison: children were presented (maximum 2s) with two panels –one on the left and one on the right– that contained randomly arranged sets of squares of varying sizes. In each trial participants were asked to point as fast as possible to the panel that contained more squares, and were prevented for counting. There were six test trials randomized across participants (6:9, 5:6, 6:8, 6:9, 2:5, 8:9). One additional trial (1:2) was used for practicing before starting the test. Each correct response scored one point. This task was based on previous studies assessing approximate skills in children (Halberda et al., 2008).
- Number line task: On each trial a 20cm long line was presented in the centre of a white A4 sheet. Children were asked to point to the numbers 3, 5, 6, 7, 10, and 14 in the intervals 0–10 and 0–20. The ends of the lines were thus labelled on the left by 0 and on the right by either 10 or 20. The order of presentation of the two intervals and the order of items were randomized across participants. Each trial was performed in a separate line. Before asking the participant to estimate the position of a number on the line (i.e., marking the line with a pencil), the experimenter ensured that the child was well aware of the interval size by pointing to the endpoints of the line and stating: "This line goes from 0 to 10 [20]. If here is 0 and here is 10 [20], where would you position X?" The number to be positioned in the line was orally

presented. Experimenters were allowed to repeat the number as many times as needed. The accuracy of children's estimates on the number line was calculated using the percent absolute error. This measure is frequently used to measure non-numerical estimation in children (Berteletti, Lucangeli, Piazza, Dehaene, & Zorzi, 2010; Booth & Siegler, 2006; Sella, Berteletti, Lucangeli, & Zorzi, 2015; Siegler & Booth, 2004). Lower absolute error indicates more accurate estimates.

- Everyday numerical problems consisted of seven tests meant to assess the children's ability to use numbers in situations of the daily living. The problems involved the application of basic arithmetic operations (e.g., could you show me two types of fruits or vegetables that together will make 7 pieces?), magnitude comparison (e.g., are there fewer lemons or fewer strawberries?), or money usage [e.g., "each one of these vegetables costs 1 euro. Could you bring me the box that contains the number of vegetables that will make you spend all this money (5 euros)?]. Each correct response scored one point.

5.2.4. Data Analysis

We first performed Pearson's correlation tests to determine the association between the number-related tasks and the child and family informal activities. To make sure that the relationships between those tasks were not mediated by a general cognitive or demographic factor, we computed partial correlations between the number-related tasks and the child and family activities, in which the impact of children's age, short-term verbal memory, and the SES of the family were controlled for.

Additionally, we used a stepwise regression procedure to determine which of the environmental variables predicted variation on each of the math cognition tasks. We included the numerical tests as the dependent variables and the knowledge of number information learned at home, short-term verbal memory, age, and SES of parents as potential predictors. Before running the regression analysis we checked for collinearity among predictors. Because there was a high collinearity (K =

72) we also performed a Principal component analysis to obtain a new set of uncorrelated predictors to feed the regression. Because the results of the regressions using PCA yielded virtually the same results of the regression that used the original predictors, only the latter are reported.

5.3. RESULTS

5.3.1. DESCRIPTIVE STATISTICS

The mean percentage of errors was 14% (range 0–75%) in the counting task, 22% (range 0–80%) in the one-to-one correspondence task, 13% (range 0–67%) in the magnitude comparison task, and 25% (range 0–75%) in everyday numerical problems. For the number line task mean percent absolute error was 21 (range 11–37%). It is worth noting that the accuracy of estimation in the number line task is similar to the one reported in comparable age groups (interval 1–10, studied by Berteletti et al., 2010, Experiment 2 = 20%; interval 1–20 = 15%).

5.3.2. CORRELATIONAL RESULTS

The results of the Pearson's correlation analysis showed that certain early numerical abilities were intercorrelated (see **Table 5.1**). The strongest correlation was observed between the children's counting abilities and their capacity to solve everyday numerical problems ($r = 0.45$; $p < 0.001$). Counting was also correlated with one-to-one correspondence tasks ($r = 0.32$; $p < 0.001$), and negatively correlated with the percent of absolute error measured in the number line task ($r = -0.31$, $p < 0.005$). The children's ability to solve everyday numerical problems was also correlated with the one-to-one correspondence task ($r = 0.29$; $p < 0.005$) and the magnitude comparison test. The latter correlation however disappeared after controlling for the children's age and verbal short-term memory, and the SES of the family.

Table 5.1 | Correlations coefficients.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
TASKS																				
1	Counting	–																		
2	Magnitude comparison	0.22	–																	
3	Everyday numerical problems	**0.45**	0.21	–																
4	Number line	***−0.31***	−0.09	−0.23	–															
5	One–one correspondence	**0.32**	0.18	***0.29***	−0.01	–														
CHILD'S KNOWLEDGE OF NUMBER RELATEDI NFORMATION																				
6	Child's answers	***0.28***	0.12	**0.34**	0.06	***0.28***	–													
7	Parent's answers	0.16	0.06	0.02	0.09	0.19	**0.33**	–												
CHILD DAILY ACTIVITIES																				
8	Videogames	−0.11	−0.11	−0.14	0.01	−0.07	0.02	−0.05	–											
9	Reading	−0.09	−0.10	−0.25	0.08	−0.01	0.02	***0.29***	−0.02	–										
10	TV watching	−0.02	−0.15	−0.19	0.06	−0.14	−0.07	0.14	**0.32**	0.15	–									
11	Sports	−0.03	−0.06	−0.03	−0.05	−0.18	0.06	0.13	0.07	0.15	−0.05	–								
12	Music	0.02	−0.07	0.06	0.09	−0.03	0.11	0.08	−0.10	−0.04	−0.13	0.02	–							
13	Other activities	0.20	0.14	0.02	−0.19	0.18	−0.02	0.13	−0.13	0.27	0.08	0.24	−0.11	–						
FAMILY DAILY ACTIVITIES																				
14	Shopping	−0.23	−0.02	−0.18	0.16	0.05	0.03	0.21	0.11	0.13	−0.08	−0.02	−0.07	0.00	–					
15	TV watching	−0.08	−0.08	−0.20	0.10	−0.22	−0.13	0.03	0.27	−0.07	**0.26**	0.10	−0.21	0.01	0.17	–				
16	Reading	0.06	0.13	0.00	0.02	−0.01	−0.01	0.13	−0.13	0.23	−0.17	0.16	0.04	0.14	0.02	0.10	–			
17	Sports	0.03	−0.09	0.05	***−0.26***	−0.06	0.08	−0.01	0.08	0.02	−0.10	**0.44**	0.22	0.05	−0.02	−0.06	0.15	–		
18	Board games	***0.31***	0.04	0.18	0.09	0.19	***0.29***	**0.40**	0.12	0.11	0.02	0.17	0.00	0.01	0.03	−0.03	0.13	−0.01	–	
19	Videogames	−0.12	−0.12	−0.15	0.00	−0.09	0.01	−0.06	**0.99**	−0.03	**0.32**	0.06	−0.11	−0.15	0.11	0.28	−0.14	0.07	0.11	–

Correlations coefficients obtained after correcting by age, memory span, SES of the family (bold $p < 0.001$; bold and italics $p < 0.005$).

The children's responses to the questionnaire inquiring into the knowledge of number related information, and the responses of the parents to the same questions were positively correlated (r = 0.33; $p < 0.001$). Moreover, the numerical information learned at home significantly correlated with the children's performance on everyday numerical problems (r = 0.34; $p < 0.001$), counting (r = 0.28; $p < 0.005$), and the one-to-one correspondence task (r = 0.28; $p < 0.005$).

Considering specific activities within the family environment, we found a positive correlation between counting and the frequency with which children played board games at home (r = 0.31, $p <$ 0.005). The frequency of playing board games also correlated with the numerical information learned at home as reported both by the parents r = 0.40, $p < 0.001$ and the children r = 0.29, $p <$ 0.005. The frequency of playing sports in family negatively correlated with the percent of absolute error measured in the number line task (r = −0.26, $p < 0.005$). Other activities did not correlate significantly with the numerical tasks.

5.3.3. *Modelling Numerical Abilities*

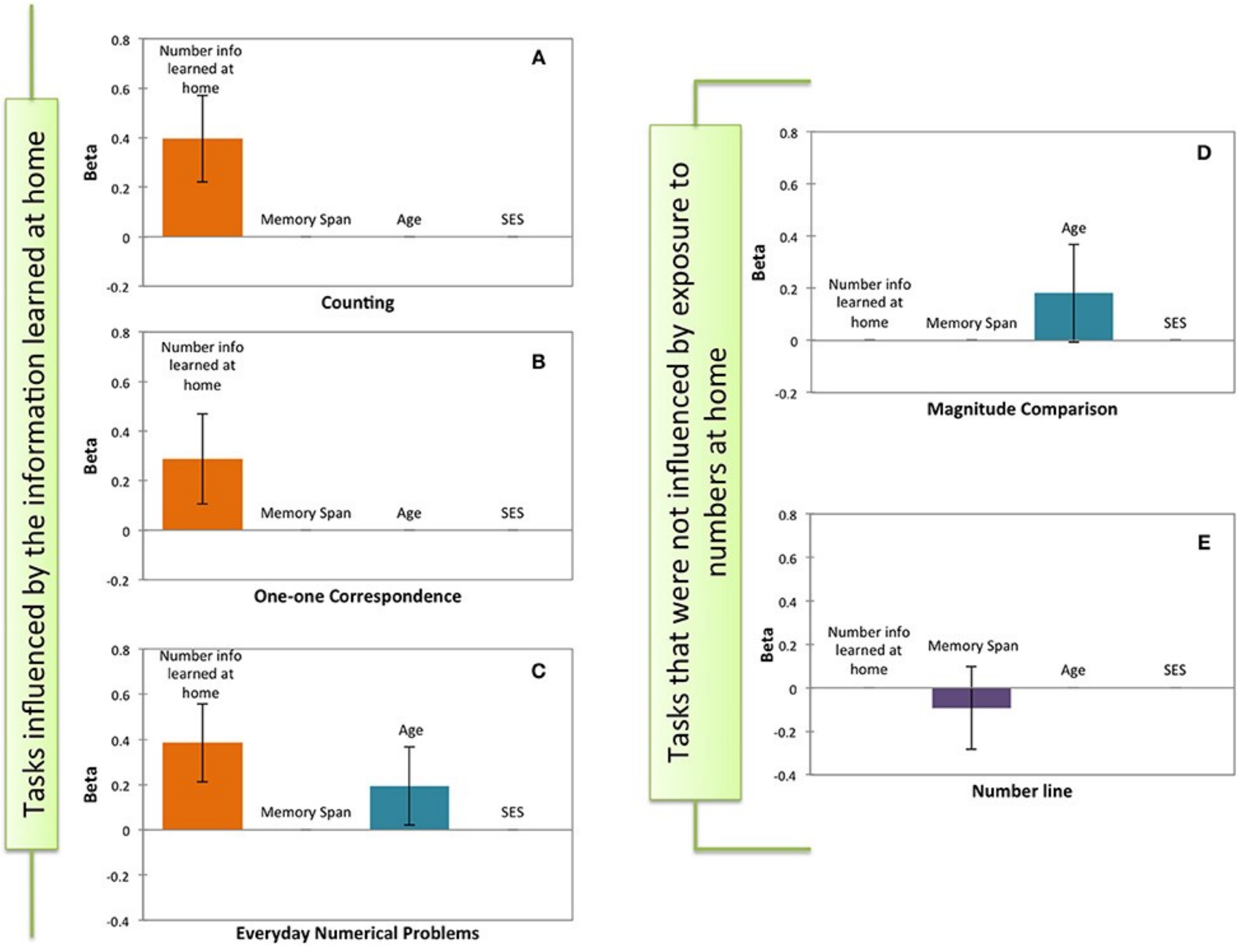
The stepwise regression with the counting ability as the dependent variable settled on a final model that included only numerical information learned at home as the actual predictor [β = 0.397; $p < 0.0001$; Model R^2 = 0.157, $F_{(1,\ 109)}$ = 20.154; $p < 0.0001$; all other Betas p's > 0.05; **Figure 5.1A**]. To avoid confounding between the predicted variable and the predictors, we excluded the counting task from the questionnaire of numerical information learned at home. We obtained virtually the same results as above. Numerical information learned at home was the only significant predictor in the final model [β = 0.352; $p < 0.001$; Model R^2 = 0.091, $F_{(1,\ 109)}$ = 11.885; $p < 0.001$; all other Betas p's > 0.05]. Similarly, numerical information learned at home predicted children's performance on one-to-one correspondence tasks [β = 0.287, $p < 0.002$; Model R^2 = 0.083, $F_{(1,\ 109)}$ = 9.728, $p < 0.002$; all other Betas p's > 0.05; **Figure 5.1B**] and on the everyday numerical problems (β = 0.385; $p < 0.0001$), a smaller but still significant contribution to this model was obtained with the variable age [β = 0.193; $p < 0.029$; Model R^2 = 0.188, $F_{(1,\ 109)}$ = 12.364, $p < 0.0001$]. No other variables predicted children's performance on the everyday numerical problems (Betas *p*'s > 0.05; **Figure 5.1C**). Furthermore, in the stepwise regression with children's performance on the magnitude comparison task as the dependent variable, a trend emerged for age as predicting factor [$\beta = 0.181$; $p = 0.058$; Model $R^2 = 0.033$, $F_{(1, 109)} = 3.676$; $p < 0.058$; all other Betas *p*'s > 0.05; **Figure 5.1D**]. Nearly the same results were found after excluding the pair that could be solved with subitizing strategies (i.e., 2:5): ($\beta = 0.103$; $p = 0.057$; all other Betas *p*'s > 0.05). Moreover, when considering only the items that could be at the critical ratio for 5–6 year-olds (i.e., 5:6, 8:9), the factor age became a significant predictor in the magnitude comparison task [$\beta = 0.304$; $p = 0.006$; Model $R^2 = 0.064$, $F_{(1, 109)} = 7.690$; $p = 0.006$; all other Betas *p*'s > 0.05] [see Halberda and Feigenson (2008) for critical rations at these ages]. Finally, none of the other variables predicted children's performance on the number line task [Model $R^2 = 0.009$, $F_{(1, 109)} = 0.938$; $p = 0.335$; **Figure 5.1E**].

5.4. Discussion

In the current study, we explored whether activities within the family environment and numerical information learned at home relate to pre-schoolers' performance on different numerical tasks. The main question was whether numerical instruction embedded in real-life settings influences tasks that depend on approximate representations, on exact representations, or both.

The findings indicate that the early acquisition of numerical information within the family environment significantly predicts the children's ability to solve numerical problems in everyday situations, counting abilities, and the skills for identifying one-to-one correspondences between sets. Crucially, not every numerical skill was related to the acquisition of numerical information at home. Children's performance on number line or magnitude comparison tasks, that essentially tap the approximate system, were not predicted by the amount of numerical information learned in the family environment.

Figure 5.1 | Significant predictors of the stepwise regressions performed on each mathematical test.



(A) Counting. (B) One-to-one Correspondence. (C) Everyday numerical Problems. (D) Magnitude Comparison. (E) Number line test. The y-axis depicts the standardized scores (β) of the predictors in each the model. The x-axis shows the potential predictors: Number Information Learned at Home, Memory Span, Age, and SES. Error bars indicate 95% confidence intervals.

These findings are in agreement with previous studies showing a relation between numerical instruction at home and children's math performance (e.g., Anders et al., 2012; LeFevre et al., 2009). These data also extend previous research in several ways. First, the results show that the children's performance in numerical tests relates to the acquisition of numerical knowledge of everyday facts (e.g., ages, birthdates, phone numbers, etc.), not just to direct mathematical instruction by parents, such as teaching how to count (Blevins-Knabe & Musun-Miller, 1996; Pan et al., 2006), or add (Huntsinger et al., 2000; LeFevre et al., 2002). Second, our study shows that numerical information learned at home also predicts the children's ability to solve simple word problems containing arithmetic operations that they have not formally learned at this age. Third, our findings suggest that numerical information learned at home affects tasks involving exact representations of number. By contrast, this knowledge does not affect tasks that depend on approximate representations, such as magnitude comparison and number line estimation. For magnitude comparison, Piazza et al. (2013) found that formal education is correlated with better performance in the Munduruku, an Amazonian tribe without words for exact counting. Park and Brannon (2013) found that training improved both comparison performance and maths ability. However, both of these studies used adult subjects. Another study of adults by Cappelletti et al. (2013), found that training improved magnitude comparison but the improvement did not transfer to arithmetic performance. Thus, it would seem that while the magnitude comparison is trainable, it does not get trained by numerical activities in the home in young children. The effects on exact number tasks are therefore not mediated by the approximate number system in our study.

The numerical information learned at home had a large effect on the counting ability of the children, and this appears fundamental to arithmetic learning. For example, Geary and colleagues showed that individual differences in first graders' counting abilities correlated positively with differences in their arithmetic proficiency (Geary et al., 1992). A similar pattern of results was found by Aunola et al. (2004) in a longitudinal study. The authors identified the counting ability at preschool age as a reliable predictor of mathematical achievement in first grade. Moreover Passolunghi et al. (2007) also identified counting skills at the beginning of primary school as a direct precursor of mathematical learning 6 months later. Furthermore, in Reeve et al. (2012), the ability to exactly enumerate sets in kindergarten predicted age-appropriate arithmetical attainment at every year until age 11, when their longitudinal study ended.

The fact that parents' answers regarding children's knowledge of information did not correlate well with their children's performance on the test is not at all surprising. It supports previous views suggesting that children's accounts might be more informative than parental ones. It has been argued that, particularly in the mathematical domain, parents may miss a lot of activities, those when they are busy with other things, or when the child is at some distance from the parent (Tudge

& Doucet, 2004). Reliance on parental accounts, rather than direct observations of, or conversations with, children also has the disadvantage that children's own experiences are devalued (Hogan, Etz, & Tudge, 1999). It has been shown that parents are generally more concerned with specific aspects of their children's cognitive development than others. Their teaching in some domains might be genuinely incidental whereas for other domains they make deliberate efforts to teach their own children. Those activities on which the parents focus more are therefore reported more reliably. LeFevre et al. (2009) showed, for example that the frequency with which parents reported storybook reading is considerably higher than the frequency of playing board or card games. This focus could be due to the parents' personal preferences, their priorities, or both. In any case they seem to affect the parents' ratings about activities of the children in other domains.

The present data also show a positive correlation between the frequency with which children performed specific activities within the family environment and their numerical abilities. In particular the results showed a correlation between the frequency with which children practiced sports and their performance in the number line task, which might be due to the common involvement of spatial abilities in both activities. Moreover, there was a correlation between the frequency with which children played board games at home, their knowledge of number related information and their counting abilities. These results add to the body of literature on early numerical cognition, providing evidence that playing board games correlates with the development of numerical skills in children (LeFevre et al., 2009; Ramani & Siegler, 2008). Board games require children to remember numbers and to exercise the counting procedure, therefore contributing to the enhancement of this numerical ability. These results are partially consistent with a previous study of Ramani and Siegler (2008) addressing the effects of playing board games over numerical development. This study showed that a 2 weeks board game program improved children's counting abilities and also the children's performance in numerical magnitude comparison and number line estimation. Consistent with their results, we found a correlation between the frequency of board game playing and the children's counting abilities. However, our results showed no correlation between the frequency of playing board games at home and either magnitude comparison or number line estimation. This discrepancy might be due to the differences in the intensity and type of the exposure. Whereas Ramani and Siegler exposed children to an intensive training with a single game, our study focused on playing board games in the family environment (not solely games designed to improve number line estimation). Additionally, while Ramani and Siegler found these environmental effects on children from low-SES, our study grouped children coming from a wide range of socio-economic backgrounds. Thus, another possibility is that the SES of the families modulates the effects of board games over numerical representations, in the same way the SES modulates interventions over early language skills (Hurtado, Marchman, & Fernald, 2008) and cognitive development (Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003).

The current results showing differential correlations between numerical knowledge acquired at home and each of the two numerical systems, questions the possibility that the exact and the approximate representations are interconnected, at least in this particular group. If the exact representations linked to the approximate system, one would expect parallel effects on both approximate representations and exact representations. Instead, we found that children who knew more number-related information only showed better exact representations; the same association was not apparent or transferred to the approximate system. Results from previous studies are in agreement with these findings. Using highly controlled training programs for children on either exact or approximate skills, Obersteiner and colleagues showed that participants improved only the skill trained with no crossover effects (Obersteiner, Reiss, & Ufer, 2013). Additionally, Mussolin et al. (2012) found an association between tasks depending on approximate number system and the symbolic abilities in 3- to 4-year-old children, but such association was absent in the group of 5- to 6-year-olds that was comparable to the age of children in our sample. It is thus possible that the interactions between the two representational systems may change across development. However, it is also possible that the links between the two representational systems are present at different ages but become evident only longitudinally. This is an open question that requires further exploration.

The question arises at to the limits of the information learned at home and activities within the family environment as potential modulators of the children's numerical skills. Are younger children, who generally spend more time at home, more susceptible to the numerical activities within the family environment than older children? Is there a critical period after which these activities do not impact significantly the children's representations of numbers? While the current study focused on 5- to 6-year-old children's numerical abilities, future studies with children at different ages should be able to establish whether, for instance, earlier numerical experiences can provide cascading advantages to the young math learner. A comprehensive exploration of the developmental trajectories of different numerical abilities (e.g., counting, estimation, magnitude comparison) and their interaction with everyday exposure to numbers should contribute to further clarify these issues. Such information will be also crucial for identifying temporal windows in which interventions for children at risk might be more effective.

To summarize, the present study sheds light on the way numerical information acquired at home links to numerical representations in 5–6 years-old children. It is pointed out that the development of certain basic numerical concepts is associated with the amount of numerical facts acquired at home and the frequency with which children carry out specific activities within the family environment. In particular, the data suggests that early mathematical concepts associated with exact—but not approximate—representations can be enhanced when learning numerical information takes place in real-life activities at home.

5.5. Limitations

At this point of our research it is not possible to identify the directionality of the correlations between numerical information learned at home and children's performance on certain numerical tests. One possibility is that children with higher intrinsic mathematical abilities demand more numerical information from the family environment. However, these results could also suggest that the frequent use of numbers in familiar interactions enhances children's numerical knowledge.

Although it seems likely that a regular exposure to numerical information boosts basic numerical understanding in young children, more research is needed to determine the directionality of the influences that occur between intrinsic numerical abilities and family factors.

Another limitation of the work regards the extent to which the numerical information learned at home interacts with the information acquired in other institutions. Although current pre-school programs in Italy are not concerned with teaching birthdates, age, phone numbers of the family members, number of brothers, etc. we do not exclude the possibility that other number related everyday knowledge might be consolidated in this environment.

Finally, we obtained information about the specific board games the children played at home. All Italian parents who reported their children playing board games mentioned numerical games such as "tombola," "uno," "carte," but also non-numerical games such as memory or puzzles. The time invested in each of these types of games was not assessed; however this information might be important to determine the nature of the games that significantly influence numerical understanding.

CHAPTER II

Study 6: Numerical Activities of Daily Living - Financial (NADL–F): A tool for the assessment of financial capacities

(Under review in Journal of Alzheimer's Disease)

6.1. INTRODUCTION

Financial capacity has recently been defined as "the capacity to manage money and financial assets in ways that meet a person's needs and which are consistent with his/her values and self-interest" (Marson, Hebert, & Solomon, 2012). The loss of this capacity can have serious consequences on the individual (Griffith et al., 2003; Marson, 2013; Marson et al., 2000); this might be related to significant changes in the person's psychological condition, and questions the person's individual autonomy, which is fundamental for wellbeing. Legally, a person that is judged as unable to look after his/her own finances and estate is often assigned a financial guardian.

The social consequences of maintaining financial abilities are also of pivotal importance. Life expectancy has increased in recent decades in wealthy countries. However, the more the population ages, the prevalence of dementia increases, and cognitive decline is bound to also affect financial abilities (Griffith et al., 2003; Marson, 2013; Sherod et al., 2009). Moreover, older adults hold a comparatively high share of a nation's wealth. Thus, impairments in financial abilities encountered in this part of the population may also be a risk to society (Marson, 2013). For all these reasons, evaluation of an individual's ability to manage financial matters is needed.

6.1.1. THE CONCEPT OF FINANCIAL CAPACITY

Financial capacity involves a broad range of conceptual, pragmatic, and judgment abilities across various everyday settings (Marson, 2013). Different aspects of financial competence, therefore, can and probably should be considered separately (Grisso, 1986). In fact, a given individual can be able to perform simple purchases at a grocery store, but not to make important financial judgments (or vice versa). Moving from such considerations, complex instruments taking into account the multidimensional aspect of financial capacity have been proposed (Darzins, Molloy, & Strang, 2004; Kershaw & Webber, 2004, 2008; Okonkwo et al., 2006; Webber et al., 2002). Not surprisingly, the clinical conceptual models that have inspired the construction of such instruments differ considerably on from another (Marson, 2015). Some of the models are based on traditional neuropsychological principles (Moye & Marson, 2007), others focus on the importance of real word applications (National Academies of Sciences Engineering and Medicine, 2016) and independence of the patients (Marson et al., 2000; National Academies of Sciences Engineering and Medicine, 2016), yet others point to decision making abilities as the fundamental skill at the basis of financial capacity (Lai et al., 2008; Lichtenberg et al., 2015). One of the few tests for which psychometric properties and analyses on validity on a normative sample are available is the Financial Competence Assessment Inventory (FCAI) test (Kershaw & Webber, 2008). The FCAI is commercially distributed, which limits its use for clinical and research purposes, however. Probably the most popular and widely used tool is the 'Financial Capacity Instrument (FCI) (Marson et al., 2000) that conceives financial capacities as a broad set of clinically relevant skills and activities necessary for independent functioning in the community. Theoretically, the model groups these activities into two basic dimensions: a) performance (e.g. counting coins, paying bills) and b) judgment (e.g. make investments, choose the better offer). Practically, the implementation of the model provides three levels of analysis: tasks, domains, and general scores (Marson et al., 2000). The FCI assesses a broad range of abilities, such as basic monetary skills, financial conceptual knowledge, cash transactions, check-book management, bank statement management, financial judgment, bill payment and knowledge of personal assets/estate arrangements. Early studies using FCI (e.g., Marson et al., 2000) were mainly aimed at refining financial capacity as a theoretical construct. They involved a limited amount of participants and comprehensive norms were not provided. In later studies, however, FCI was administered to a large sample of cognitively healthy aging people, compared with people with MCI and mild Alzheimer (Sherod et al., 2009). A short form version of FCI was also validated on a large sample of cognitively healthy older people (Gerstenecker et al., 2016).

6.1.2. THE NUMERICAL ACTIVITIES OF DAILY LIVING-FINANCIAL (NADL–F)

Sharing the conceptual approach of Marson and colleagues, we developed a novel instrument to assess financial capacity in clinical populations, with the primary aim of providing a psychometrically valid tool similar to FCI to be used and adapted in a European environment. Thus, with the NADL–F we do not propose a new conceptual model on financial capacities but to take into consideration the considerable differences that are necessary to define "independent financial functioning" in the various socio-cultural contexts. Considering this, the tasks we developed (selected by the authors after literature review (Kershaw & Webber, 2008; Marson et al., 2000) and discussion with clinicians) assess a wide range of topics that are mostly relevant in clinical practice: "Is the patient able to shop at the grocery store? Is the patient able to understand what a salary is? Is the patient able to make financial choices?" Moreover, it comprises domains largely overlapping with those included in previous tests (Kershaw & Webber, 2008; Marson et al., 2000): basic monetary skills, such as counting coins, the ability to shop and make mental calculations while shopping, the ability to manage home bills, and the ability to detect fraud. Other domains, considered in previous tests, were not included, though: for example we decided not to include a assets/estate arrangements (as in FCI (Marson et al., 2000)), real estate personal transactions are much less common than in the United States.

Following previous works (Kershaw & Webber, 2008; Marson et al., 2000), NADL–F mainly includes performance-based tasks that simulate real life situations. All the tasks, while being ecological, have an item structure and a scoring system that is similar to traditional neuropsychological tasks, that should facilitate clinical assessment (e.g., item to be read aloud by the clinician with a score of 0 for incorrect responses and of 1 for correct responses). Moreover, NADL–F provides cut-offs based on a healthy control sample, and has practical applicability in several clinical populations, as well as reasonably short administration time (45-60 minutes). To encourage the use of the test in clinical settings and adaptation to other languages and cultures, we include the NADL–F battery as Appendix B. To assess the construct validity of NADL–F we correlated the performance in the test with other neuropsychological tests. In this analysis we are particularly interested in the correlation of NADL–F performance with tests on numerical competence. In fact, recent studies highlighted the importance of numerical abilities in daily living (Benavides-Varela et al., 2015) and suggest that basic mathematical abilities may be relevant predictors of financial capacities (Martin et al., 2012; Sherod et al., 2009). Importantly, Sherod and colleagues (Sherod et al., 2009) found that written arithmetical skills was the primary predictor of financial capacity across the Dementia spectrum, while executive functions and verbal memory showed a secondary influence on performance. We planned to replicate this investigation with NADL–F, by correlating the performance on NADL–F with the performance on NADL (Numerical Activities of Daily Living −Semenza et al., 2014), a tool that that was not specifically designed to assess financial abilities but encompasses the assessment of all basic aspects of math ability as well as their impact on daily life. In this way we can start to understand which basic mathematical ability is recruited for more complex aspects of financial capacity. Importantly, a careful and detailed assessment of Financial Capacities and of related cognitive abilities (as basic numerical competence) is a fundamental preliminary step in view of. the development and goal setting of focused treatment protocols. The administration before and after treatment of NADL-F will meet the needs of such assessment.

6.2. METHOD

6.2.1. PARTICIPANTS

We administered the NADL–F test to 91 patients with neurological disorders and 120 healthy participants. The healthy control group (69 male, 51 female) had a mean age of 69.43 years (*SD* = 8.40) and a mean education of 12.2 years (*SD* = 4.80). All healthy controls were autonomous in their activities of daily living, and had no relevant pathologies that could affect their cognitive performance. They did not present with developmental learning disorders. All of them received either Mini-Mental State Examination (MMSE −Folstein et al., 1975) or Montreal Cognitive Assessment (MoCA −Nasreddine et al., 2005) and had a performance above cut-off.

The patient group included people with heterogeneous neurological disorders. Following the rationale already adopted for the validation study of NADL (Semenza et al., 2014), we collected data on a wide variety of pathological conditions, focusing on those that are expected to show impairment in financial abilities. This strategy ensured variability in the data (as control participants are expected to score almost at ceiling level), thus allowing a meaningful investigation of the psychometric properties of the test.

The patients' diagnoses were made by experienced neurologists according to clinical standard criteria (e.g., Mild Cognitive Impairment, MCI) patients were classified according to the criteria reported by Gauthier et al. (2006): they had subjective complain of memory loss, impaired performance in structured memory tests, they were not demented and they were generally intact in their activities of daily living. The aetiology of these patients was not known at the time of the study, and none of them had a medical condition (e.g. vascular accident, metabolic disorder) that could be the direct cause of the MCI status. Patients were recruited in three centres across northern Italy. All MCI patients were recruited at I.R.C.C.S. San Camillo Hospital Foundation in Venice, and Stroke and Parkinson participants were recruited at San Camillo Hospital in Torino. All remaining patients were recruited at and at University Hospital of Padova. Data on the patient group are summarized in **Table 6.1**.

All participants took part in the study on a voluntary basis and gave their informed consent according to the Helsinki Declaration. The study was approved from a local ethical committee.

Table 6.1 | Demographical variables of patients included in the study of psychometric properties of NADL−F.

Pathology	Age (*SD*)	Education (*SD*)	Gender (n female/male)	N
MCI	74.88 (6.74)	10.94 (4.67)	24/28	51
Cerebral Stroke	66.33 (7.13)	10.87 (5.10)	7/8	15
Parkinson Disease	67.41 (7.80)	10.94 (5.01)	5/12	17
Others	68.75 (15.13)	8.37 (3.70)	5/3	8

This tableshows the main demographic data of the patient group. The group labeled as "Others" included patients with heterogeneous pathologies: one patient with cerebellar damage, one patient with corticobasal degeneration, one patient with Hashimoto's encephalopathy, one patient with multiple intraparenchimal lesions, two patients with comorbidity of MCI and stroke, one patient with a diffuse vasculopathy, and one patient with an extrapyramidal syndrome.

6.2.2. MATERIALS

The NADL–F test

The final version of NADL–F test was composed of seven tasks[1] assessing different aspects of financial capacity. All tasks included several items, designed to be of increasing difficulty when possible.

[1] The initial version of NADL−F comprised a total of ten tasks. Three tasks: Price Knowledge, Guided Purchase, and Financial Planning were not included in the final version, since they showed unsatisfactory psychometric properties, especially because of the internal consistency of items. For this reason, these tasks are not further analysed in the manuscript.

Task 1) Counting Currencies

In this task the participant was asked to count given amounts of currencies (replication of real euro banknotes or coins) or to select a specific quantity of money from a given amount. This task aimed to evaluate if the participant is familiar with the euro currency and was able to perform simple mental calculations, analogous to those involved in simple cash transactions but in a simplified setting.

Task 2) Reading Abilities

In this task the participant was asked to read, transcode, and manipulate written information (mainly written numbers) presented in ecological contexts, such as replication of bills or of checks. The aim of this task is to evaluate if the participant is able to deal with written information about money in everyday life situations.

Task 3) Item Purchase

In this task the participant was asked to simulate some purchases in a shop, buying one or more items. They were asked to pay the correct amount and to check if the correct change is given after the payment. The aim of this task was to evaluate the ability of the participant to deal with operations (calculations, keeping in mind the relevant information) that are necessary to make cash transactions during shopping in real life.

Task 4) Percentages

This task consisted of a series of questions on percentages, presented as real life concrete examples. The aim of this task was to investigate if the participant is able to perform the mental calculations needed in percentages.

Task 5) Financial Concepts

In this task the participant was asked to define a series of concepts related to financial capacity (e.g. salary, IBAN). The aim of this task was to investigate the participant's knowledge of financial concepts that are more relevant to the Italian cultural context.

Task 6) Bill Payments

This task consisted of different items, all related to the practical and conceptual ability of dealing with home bills (e.g., telephone, electric current). It aimed to specifically evaluate managing bills, which is one of the most relevant domains demonstrating financial independence in the Italian sociocultural context.

Task 7) Financial Judgments

In this task the participant was presented with a series of hypothetical scenarios, in which an agent performs a financial choice. Only a third of the scenarios contributed to the final score, whereas the others acted as fillers. In the relevant scenarios the main character was often the victim of a fraud (the most common types of fraud were included). The aim of this task was mainly to evaluate whether the participant was able to make meaningful financial judgments and detect fraudulent behaviours. The filler scenarios were included to distract the participants from the aim of the task.

The NADL–F Interview

This interview was designed to investigate the awareness of an individual's financial capacity. The interview was composed of several questions reflecting the same aspects evaluated in the NADL–F tasks. For example, for the Counting Currencies task the participant was presented with a series of sentences such as "are you able to count coins or to give the correct change", "Do you recognize coins?”, etc. In the interview there was no correct or wrong answer: participants are asked to rate if they were capable of performing the described activity autonomously, capable with external aid, or if they were not capable (similary to Wadley, Harrell, & Marson, 2003).

Other Neuropsychological tasks

Together with the NADL–F a subset of participants (n = 59, 65% participants from the patient group and n = 88, 73% participants from the healthy control group) performed a series of additional neuropsychological tasks and clinical scales to investigate the relationship between NADL–F performance and other cognitive or clinical constructs[2].

We administered the following tests: the MMSE (Folstein et al., 1975) as a measure of general cognitive status, the Forward and Backward Digit Span (Monaco, Costa, Caltagirone, & Carlesimo, 2013) as a measure of short term and working memory, the Rey Auditory Verbal Learning Test (RAVLT) as measure of memory and learning (Novelli et al., 1986), the Phonemic Fluency test as a measure of executive function efficiency (Novelli et al., 1986), the Cognitive Reserve Index-questionnaire (CRI-q −Nucci et al., 2012) as a measure of cognitive reserve, the Geriatric Depression Scale as a measure of depression (Segulin & Deponte, 2007), and the Instrumental Activity of Daily Living (IADL −Katz, 1983; Lawton & Brody, 1969) as a known scale to evaluate activities of daily living, which partly overlaps with domains measured by the NADL–F. Finally we administered the Numerical Activities of Daily Living (NADL −Semenza et al., 2014) as a measure of numerical abilities and their relevance in everyday life.

6.2.3. Procedure

All participants were evaluated by trained neuropsychologists. The tests were administered in a fixed order, starting with the NADL–F interview followed by all the NADL–F tasks. The order of

[2] These tests were part of a larger battery administered to the patients for clinical purposes.

the tasks was: Counting Currencies, Reading Abilities, Item Purchase, Percentages, Financial Concepts, Bills payment, Financial Judgments. All other neuropsychological tests were administered after the NADL–F tasks.

Statistical analyses

The final version of NADL–F was defined after an initial item analysis, performed according to the Classical Test Theory. The aim of the item analysis was to identify and select satisfactory tasks and items, and to shorten the test. First of all, items that showed no or very low variability (i.e., a ceiling or floor effects) were discarded. Then each task was analysed separately. In the 91 patients the internal consistency of each task was investigated separately. Items with low r-drop (i.e., the correlation between the item and the task total, excluding that item) were removed, to reach a Cronbach’s alpha above a threshold of 0.55. After this, we evaluated whether the selected items showed good internal consistency also among healthy controls. Only tasks and items that were satisfactory both for patients and controls were included, resulting in at least 5 items per task for the final version of NADL–F.

After the item analysis, reliability of NADL–F was further investigated assessing test-retest reliability (Pearson’s correlations) and inter-rater reliability (Intra-class correlations), performed on a subset of participants.

The same item analysis of the NADL–F tasks was performed on the NADL–F interview, and results on this section of the NADL–F interview were correlated with corresponding tasks of NADL–F, by means of Pearson’s correlations.

To assess construct validity, first a factor analysis on NADL–F using total scores of each task was performed. Total scores of the NADL–F task were correlated with the other neuropsychological tests administered and with the scores of NADL (Semenza et al., 2014), using Pearson’s correlations with Bonferroni correction for multiple comparisons.

To investigate the effect of age, gender and education on NADL–F tasks, we performed a series of multiple regressions with each NADL–F task score as dependent variable. This analysis was restricted to healthy controls, as the results of these regression models were used to build cut-offs for NADL–F tasks.

Age and education were included in the regressions as continuous predictors, whereas gender was dichotomized. For each regression, the following regression modelling strategy was adopted: starting from an initial model including the three predictors (Age, Education and Gender), terms were backward eliminated with a method based on Akaike Information Criterion (AIC), using the step function of R (R Development Core Team, 2012). After this first selection, the terms whose coefficients were not statistically significant were removed. Following the procedure already used in Arcara & Bambini (2016), we explored the possibility of improving the fit by allowing non-linear terms: a graphical inspection of the partial residuals of each variable in each model was performed to investigate if including non-linear terms (e.g. quadratic terms) could improve the model fit of the data. For all the variables that showed a non-linear trend, we tested whether adding quadratic terms, cubic terms, or restricted cubic splines yielded better models. Restricted cubic splines are cubic splines (i.e., a cubic function to account for non-linearity) that are adjusted to avoid overfitting for the more extreme values of the continuous predictors.

According to the standard regression procedure, if a quadratic term (or a cubic spline) is significant, the linear term in the model is also kept, regardless of its significance. In some cases including a non-linear predictor led to a change in the estimate of a previously significant predictor (for example, if including a quadratic term for education changed the estimate of age effects, with the latter becoming non-significant). In such cases, the AIC of the models were compared and the model with the lowest AIC was chosen.

Cut-offs of normality were obtained from healthy control data by means of the regression method of (Crawford & Garthwaite, 2006), and using the results of the regressions to take into account the effect of demographic variables.

6.3. RESULTS

The NADL–F tasks were easily understood and performed by all participants in both groups. Descriptive statistics for the healthy control group and the patient group (as a whole) are reported in **Table 6.2** and **Table 6.3**. Detailed tables stratified by age and education are reported in the Supplementary Material 6 – data tables and cut-offs.

Table 6.2 | Descriptive statistics of NADL−F tasks for the healthy control group.

Task	Mean	*SD*	Median	min	max	Kurtosis	Skewness	Q1	Q3
Counting Currencies	4.73	0.73	5	1	5	11.45	−3.27	5	5
Reading Abilities	6.35	1	7	2	7	5.32	−2.13	6	7
Purchase	12.53	2.04	13	3	14	5.23	−2.11	12	14
Percentages	6.62	2.26	7	0	9	−0.06	−0.9	5	8
Financial Concepts	8.85	2.48	9	3	14	−0.73	0.06	7	11
Bill Payments	4.83	1.18	5	1	6	0.39	−0.97	4	6
Financial Judgements	5.49	0.94	6	2	6	3.68	−2.01	5	6

This table reports the means, standard deviations, median, minimum, maximum, kurtosis, skewness, first quartile, and third quartile for NADL−F scores in the group of 120 healthy controls.

Table 6.3 | Descriptive statistics of NADL−F tasks for the patient group.

Task	Mean	*SD*	Median	min	max	Kurtosis	Skewness	Q1	Q3
Counting Currencies	4.26	1.07	5	1	5	1.4	−1.49	4	5
Reading Abilities	5.64	1.49	6	1	7	0.7	−1.15	5	7
Purchase	11.41	2.51	12	2	14	1.79	−1.25	10	13.75
Percentages	5.34	2.28	5	0	9	−0.86	−0.3	4	7
Financial Concepts	6.91	2.52	7	1	14	−0.1	0.26	5	8
Bill Payments	3.84	1.35	4	0	6	−0.23	−0.32	3	5
Financial Judgements	5.1	1.25	6	1	6	1.23	−1.44	5	6

This table reports the means, standard deviations, median, minimum, maximum, kurtosis, skewness, first quartile, and third quartile for NADL−F scores in the group of 91 patients with heterogeneous pathologies.

6.3.1. ITEM SELECTION AND INTERNAL CONSISTENCY

Results on Internal consistency of NADL–F are reported in **Table 6.4**.

The final version of NADL–F included the following tasks: Counting Currencies, Reading Abilities, Purchase, Percentages, Financial Concepts, Bill Payments, Financial Judgments. According to a commonly used rule-of-thumb to evaluate alpha coefficients, NADL–F shows mostly adequate or marginally adequate internal consistency. The relatively low scores, however, are not uncommon in neuropsychological tests (Slick, 2006) and resemble the values already obtained in the other available test on Numerical Activities of Daily living (Semenza et al., 2014).

Table 6.4 | Internal Consistency of NADL−F tasks.

	Alpha		
Task	**Patients**	**Controls**	**Total**
Counting Currencies	0.62	0.64	0.62
Reading Abilities	0.67	0.60	0.66
Purchase	0.75	0.78	0.77
Percentages	0.70	0.74	0.74
Financial Concepts	0.61	0.59	0.64
Bill Payments	0.58	0.62	0.65
Financial Judgments	0.63	0.55	0.61

This table reports the internal consistency of the NADL−F tasks (Cronbach's alpha, standardized). The first column report values for the analysis in the patient group, the second columns report the values for the analysis in the healthy control group, and the third column report the values for the analysis on both patients and healthy controls.

6.3.2. TEST-RETEST AND INTER-RATER RELIABILITY

Test-retest was assessed in a subset of 18 participants. Thirteen controls and 5 patients with MCI were administered the NADL–F twice, with an average period of 2-4 months between the two assessments. The short test-retest interval was chosen to avoid the detrimental effect of cognitive decline in the MCI group. The Pearson correlation coefficient was used as measure of test-retest reliability. In the analysis of inter-rater reliability 14 participants (9 patients with MCI and 4 healthy controls) were tested by two examiners, who separately scored the same performance. The Single-rater Intra-class correlation coefficient was used as measure of inter-rater reliability. Results of test-retest and of inter-rater reliability are summarized in **Table 6.5**.

Table 6.5 | Test-retest reliability and Inter-rater reliability of NADL−F tasks.

Task	Test-retest reliability (Pearson Correlation)	Inter-rater reliability (Intra-Class correlation)
Counting Currencies	0.62	0.64
Reading Abilities	0.67	0.60
Purchase	0.75	0.78
Percentages	0.70	0.74
Financial Concepts	0.61	0.59
Bill Payments	0.58	0.62
Financial Judgments	0.63	0.55

This table reports the test-retest reliability and the inter-rater reliability for each NADL−F task.

6.3.3. Analysis on NADL–F interview

To analyse the interview we first performed an item analysis on all the interview items, adopting the same approach used for the NADL–F tasks. After this procedure four items were discarded. The remaining items showed acceptable consistency [Cronbach's alpha for patient group = 0.61; Cronbach's alpha for control group = 0.70; Cronbach's alpha for all participants = 0.6]. Test-retest and inter-rater reliability were assessed in small subsamples (n = 5 and n = 7, respectively). The NADL–F Interview showed low test-retest reliability (r = 0.44) and good inter-rater reliability (ICC = 0.84). We then investigated the relation between the NADL–F interview and the NADL–F tasks, by correlating the performance on each NADL–F task with the items in the interview that referred to the same task (for example, by correlating the performance in the Counting Currencies task with the score derived from items in the interview addressing whether the participant is able to count coins). The resulting correlations were moderate in some cases and low in other cases [Counting currencies, r (93) = 0.02, $p = 0.85$; Reading Abilities, r (93) = 0.21, $p = 0.04$; Item Purchase, r(93) = −0.07, $p = 0.47$; Percentages, r (92) = 0.33, $p = 0.001$; Financial Judgments, r(93) = 0.22, $p = 0.03$].

6.3.4. Validity

As NADL–F is the first neuropsychological test of Financial Abilities available in Italian, it is not possible test the validity of NADL–F by comparing with a gold standard. To ensure that the test is valid for assessing Financial Abilities, we first focused on content validity, by designing tasks that reflect the current standards for testing Financial Abilities (Kershaw & Webber, 2008; Marson et al., 2000). Then we investigated the construct validity in two ways: by examining the relationship of NADL–F tasks relationships and the correlation between NADL-tasks and other tests that are expected to correlate with the Financial Abilities.

Construct Validity (1). Factor Analysis

To analyze the relationship between NADL–F tasks we performed an exploratory factor analysis on the total scores of the NADL–F tasks. The aim of this factor analysis was to investigate the correlations between tests, and to see if a meaningful pattern of relationships emerged. We did not expect that the analysis would capture a separate factor for each task, rather that it would extract a limited number of factors related to the common cognitive correlates of the tasks. Data from both patients and controls were combined to maximize sample size and variability (119 controls and 87 patients, four patients were discarded because of missing values). A preliminary Bartlett's sphericity test on the data was significant, suggesting it was appropriate to perform a factor analysis [$\chi^2(21) = 595.25$, $p < 0.001$]. The KMO value was 0.86, indicating an adequate sample size. An exploratory factor analysis (with varimax rotation) was performed and several model were compared (one, two, and three factors). The solution with three factors proved to be the best model accounting for the data, yielding the lowest Bayesian Information Criterion (BIC) value and showing satisfactory fit indices [RMSEA = 0.054; $\chi^2(8) = 11.98$, p = 0.15]. The loadings of the two resulting factors are reported in **Table 6.6**.

Table 6.6 | Factor analysis on NADL−F tasks.

Task	Factor 1	Factor 2
Counting Currencies	0.60	0.32
Reading Abilities	0.67	0.37
Purchase	0.79	0.29
Percentages	0.56	0.50
Financial Concepts	0.30	0.84
Bill Payments	0.47	0.61
Financial Judgments	0.26	0.13

This table reports the loadings on the two factors resulting from the factor analysis on NADL−F task (with varimax rotation).

An inspection of the loadings reveals that the first factor is presumably associated with the generic cognitive demands of a performance based task, such as processing speed, working memory, and attention. Indeed, the highest loading is for Percentages (which is the task that mostly requires working memory) and all tasks requiring the manipulation of several pieces of information (such as Purchase, Reading Abilities, and Counting Currencies). The second factor is presumably associated with the conceptual knowledge of financial aspects. In fact, this factor mostly loads on Financial Concepts and partly on Bill Payments, in which some items require that the patient explains what bills are.

Construct Validity (2). Correlation between NADL–F and other neuropsychological tests

In a second analysis on construct validity we examined the correlation between NADL–F tasks with other neuropsychological tests. Results are reported in **Table 6.7**. All reported values refer to Pearson pairwise correlation with p-values corrected with the Bonferroni method. These correlations were performed on a subset of 113 participants for which the data of both NADL–F and neuropsychological tests were available. This subset of participant consisted of 68 healthy controls and 45 patients (40 with MCI and 5 from the heterogeneous pathologies group). The MMSE, Backward Digit Span, RAVLT, and Phonemic Fluency test positively correlated with all tests except Financial Judgments. Forward Digit Span positively correlated with Item Purchase, Percentages, Financial Concepts, and Bill Payments. The Cri-q, an index of cognitive reserve, was positively correlated with Reading Abilities, Percentages, Financial Concepts, and Bill Payments. GDS (Geriatric Depression Scale) was not significantly correlated with the NADL–F tasks. Finally, IADL correlated with Counting Currencies, Reading Abilities, Percentages, and Financial Concepts.

Table 6.7 | Correlations between NADL−F tasks and other neuropsychological tests.

Task	MMSE	FW Digit Span	BW Digit Span	RAVLT	Phonemic Fluency	CRI-q	GDS	IADL
Counting Currencies	0.53*	0.3	0.41*	0.42*	0.44*	0.16	−0.1	0.36 *
Reading Abilities	0.38*	0.29	0.37*	0.47*	0.45*	0.44*	−0.21	0.33 *
Item Purchase	0.61*	0.36*	0.52*	0.51*	0.51*	0.23	−0.21	0.28
Percentages	0.50*	0.50*	0.53*	0.47*	0.52*	0.38*	−0.13	0.32*
Financial Concepts	0.52*	0.41*	0.44*	0.45*	0.62*	0.36*	−0.22	0.37*
Bill Payments	0.55*	0.42*	0.39*	0.58*	0.63*	0.46*	−0.16	0.29
Financial Judgements	0.25	0.17	0.13	0.26	0.29	0.04	−0.08	0.26

This table reports the r values of Pearson correlations between NADL−F task scores and other neuropsychological test scores. Stars (*) denotes significant results after Bonferroni correction for multiple comparisons.

Validity. Correlations between NADL–F and NADL.

Given the expected relation between numerical abilities and financial abilities we investigated the relationship between the performance on NADL–F task and NADL (Numerical Activities of Daily Living −Semenza et al., 2014), by means of pairwise Pearson correlations with p-values corrected with Bonferroni method. This analysis was performed on a subset of 17 healthy controls, 15 patients with MCI and two patients from the heterogeneous pathologies group. We excluded the interview with the care-giver From the NADL test (Semenza et al., 2014), given the high number of missing values in our sample. Results are reported in **Table 6.8**. Several significant correlations were found between NADL–F and NADL. The Number Comprehension task (a task of basic numerical abilities) only correlated with Reading Abilities. The Total Reading and Writing Arabic Numerals (a task on transcoding Arabic numerals), did not correlate with any of the NADL–F tasks. Mental Calculation from NADL (a task whereby the participant is required to perform a simple mental calculation) correlated with Counting and Naming Currencies, Reading Abilities, Percentages, and Financial Concepts. Rules and Principles (a NADL task tapping the knowledge of some numeric rules, as multiplication by zero, or the relation between multiplication and addition) correlated with Counting Currencies, Percentages, and Financial Concepts. The Informal Test of NADL (a short test investigating several numerical abilities in everyday life) correlated with Counting Currencies, Item Purchase, Financial Concepts, and Bill Payments. Finally, the Interview with the patient did not correlate with any NADL–F task.

Table 6.8 | Correlations between NADL−F tasks and NADL tasks.

NADL task / NADL−F task	Number Comprehension	Reading and Writing Numerals	Mental Calculation	Rules and Principles	Written Operations	Informal Test	Interview with the patient
Counting Currencies	0.45	0.15	0.66*	0.55*	0.84*	0.7*	0.24
Reading Abilities	0.59*	0.13	0.53*	0.51	0.7*	0.49	0.25
Item Purchase	0.45	0.14	0.44	0.43	0.5	0.68*	0.23
Percentages	0.4	0.28	0.66*	0.61*	0.65*	0.52	0.31
Financial Concepts	0.24	0.29	0.54*	0.71*	0.61*	0.62*	0.32
Bill Payments	0.19	0.31	0.49	0.68*	0.38	0.61*	0.46
Financial Judgements	0.16	0.42	0.13	0.34	0.17	0.21	0.27

This table reports the r values of Pearson correlations between NADL−F task scores and NADL task scores. Stars (*) denotes significant results after Bonferroni correction for multiple comparisons.

6.3.5. AGE, EDUCATION, AND GENDER EFFECTS

Results from the regression analyses are depicted in **Figure 6.1**, whereas details on the regression models are reported in **Table 6.9**.

In all NADL–F tasks a significant effect of education was found, whereas significant effects of age and gender were found only for some tasks.

Only a non-linear effect of education was found with Counting Currencies: as age increases the performance on this task increases, reaching a plateau approximately at 13 years of education. In Reading Abilities a non-linear effect of education was found: as education increases from 5 to 10 years the performance increases; then the performance is similar for participants with education from 10 to 15 years, with a slight increase after 15 years. In Purchase a negative effect of age and a positive effect of education were found: as age increases the score linearly decreases, and as education increases the score increases from 5 to 10 years, is stable from 10 to 15 years, and finally increases as the education goes from 15 to 20 years. In Percentages only an effect of education was found: as education increases, performance increases, reaching a plateau around 15 years of education. Moreover, an effect of gender was found with male participants showing better performance than females. In Financial concepts a linear effect of education was found: as education increases, the performance increases. A significant effect of gender was also found, with males performing slightly better than females. Bill Payment showed a non-linear effect of education, with better performance as education increases, reaching a plateau at 15 years of education. Finally, in Financial Judgment a positive linear effect of education was found, with higher education associated with better performance.

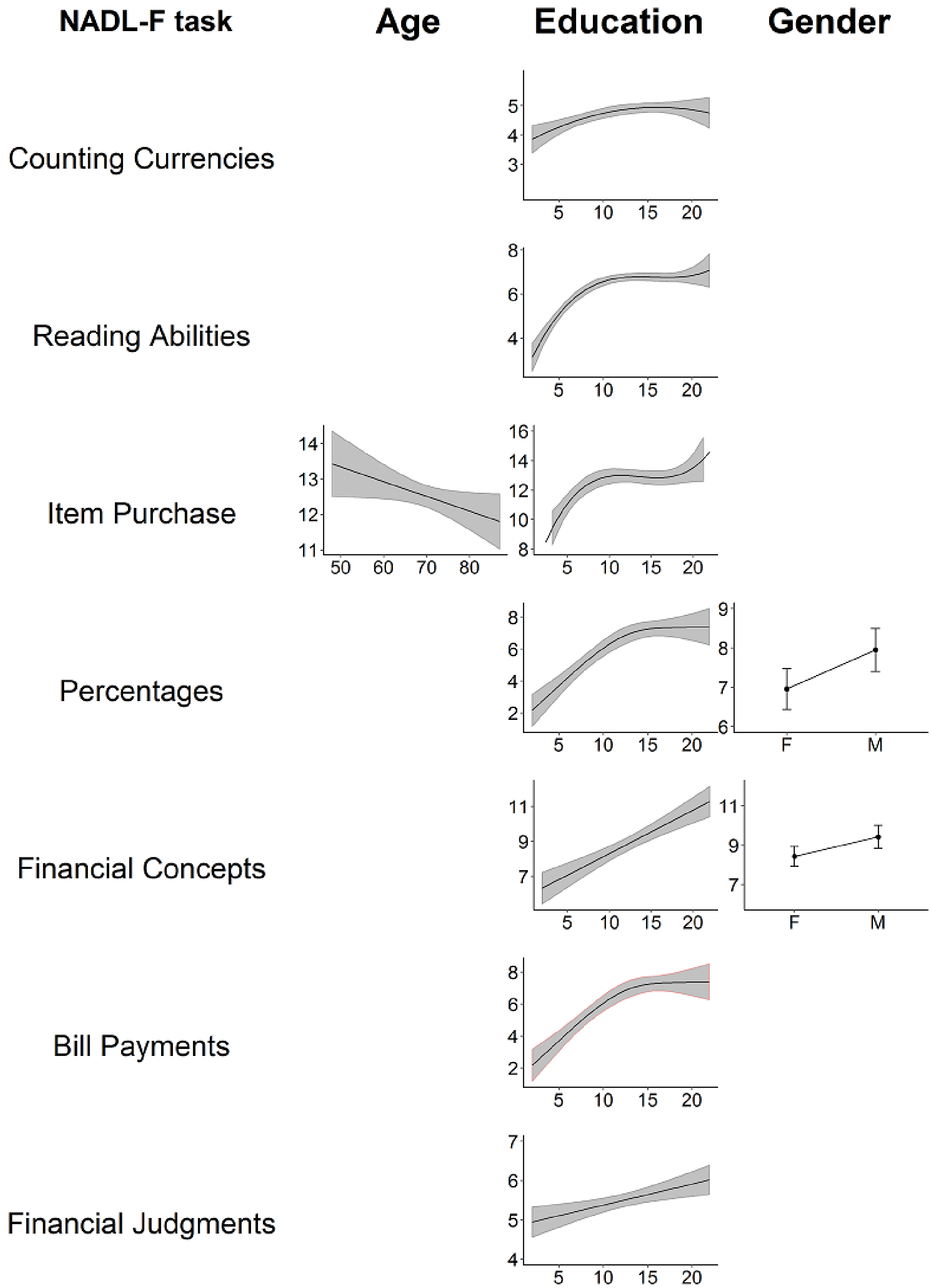
In summary, a consistent pattern was found across NADL–F tasks, with all tests showing a positive effect of education, linear for some tasks and non-linear for others. An effect of age (with worse performance as age increases) was found only in the Purchase task. Effects of gender were found in two tasks, namely Percentages and Financial Concepts: in these two tasks male participants performed better than females.

Table 6.9 | Effect of Demographic Variables on NADL−F tasks.

Task	Effect	Estimate (SE)	t-value	*p*-value	Model R^2
Counting Currencies	Intercept	3.53 (0.34)	10.28	< 0.001	0.12
	Education	0.18 (0.06)	2.79	0.006	
	$Education^2$	−0.005 (0.003)	−2.065	0.041	
Reading Abilities	Intercept	1.23 (0.63)	1.95	0.05	0.58
	Education	1.08 (0.20)	5.50	< 0.001	
	$Education^2$	−0.07 (0.02)	−3.87	< 0.001	
	$Education^3$	0.001 (0.0005)	2.96	0.003	
Item Purchase	Intercept	7.42 (2.62)	2.83	0.005	0.31
	Age	−0.04 (0.02)	−2.02	0.04	
	Education	1.95 (0.53)	3.65	0.0004	
	$Education^2$	−0.15 (0.05)	−3.05	0.003	
	$Education^3$	0.004 (0.001)	2.70	0.008	
Percentages	Intercept	1.13 (0.65)	0.64	0.55	0.45
	Education	0.51 (0.078)	6.77	< 0.001	
	rcs (Education)	−0.27 (0.08)	−3.44	< 0.001	
	Gender = Male	0.99 (0.31)	3.20	0.002	
Financial Concepts	Intercept	5.41 (0.55)	9.88	< 0.001	0.27
	Education	0.25 (0.04)	6.09	< 0.001	
	Gender = Male	0.99 (0.39)	2.52	0.01	
Bill Payments	Intercept	2.37 (0.38)	6.18	< 0.001	0.29
	Education	0.26 (0.04)	5.81	< 0.001	
	rcs (Education)	−0.16 (0.05)	−3.54	< 0.001	
Financial Judgments	Intercept	4.83 (0.23)	21.33	< 0.001	0.06
	Education	0.05 (0.02)	3.09	0.002	

This table reports the results of the regression analyses investigating the effect of demographic variables on NADL−F task scores. The following information is provided in the table: task or score name (first column); name of the term in the regression model (second column); coefficient estimate and standard error within round brackets (third column); t-value associated with the term (fourth column); p-value (fifth column); adjusted R^2 (sixth column).

Figure 6.1 | Effect of Demographic Variables on NADL−F tasks.



This figure shows the partial effects of age, education, and gender on NADL−F task scores, calculated in a regression analysis. The figure is displays NADL−F task names (first column), the effect of age (second column), education (third column), and gender. Effects not shown were not significant in the regression analyses. The black line in each plot represents the predicted score at the task. The gray bands around the lines represent point-wise confidence bands around the prediction.

6.3.6. Cut-offs

Using the data of the healthy control sample, separate Cut-offs for each NADL–F task were calculated with the regression method of (Crawford & Garthwaite, 2006). This method calculates the discrepancy between the observed and estimated score from a regression model. Cut-offs were calculated as the scores delimiting a discrepancy that is expected to be obtained by less than 5% of the population, after predicting the score from the relevant variables (age, education, and gender) (see Crawford & Garthwaite, 2006 for details on the method). In other words, a performance below the cut-off indicates that the observed performance in the patient is unexpectedly low, given his/her age, education, and gender. Hence, these cut-offs may be interpreted as the traditional cut-offs based on 5° percentile or 1.96 standard deviations below the mean, but they also have two main advantages: first, the most relevant demographic variables are entered as regressors, allowing accurate prediction of the expected score of a given individual and avoiding the arbitrary thresholds of stratified norms, second these cut-offs allow inferences to be made at the population level (and not restricted to the sample of normative data). This latter characteristic made the method of Crawford & Garthwaite (2006) preferable to traditional regression methods for corrected cut-off scores.

To calculate these cut-offs we used the same regression models built to investigate the effects of demographic variables on NADL–F task performance (see **Table 6.9**). Cut-offs are reported in the Supplementary Material 6 – data table and cut-offs.

6.4. Discussion

In this study we presented the Numerical Activities of Daily Living – Financial (NADL–F), a tool to assess financial capacities in clinical populations. This newly developed instrument proved to have overall satisfactory psychometric properties and good validity for measuring financial capacity.

NADL–F showed moderately acceptable internal consistency, with almost all Cronbach's alpha coefficients higher than 0.6. The relatively low scores in internal consistency of some tasks is not surprising given the complexity of the constructs measured, and is in line with what is observed in other tests on complex constructs related to functional abilities (see for example Kershaw & Webber, 2008; Semenza et al., 2014; and see also a larger collection of neuropsychological tests showing similar internal consistency in Strauss, Sherman, & Spreen, 2006). However these results point to the difficulty of defining unidimensional constructs on financial constructs and suggest the necessity to further refine the conceptual entities measured with the instrument. Being conservative, this result suggests that the NADL–F tasks rather than scales measuring specific theoretical constructs, should be considered as results on a collection of item replicating ecological activities that are relevant to investigate financial capacities in clinical contexts. Results on test-retest and inter-rater reliability indicate that the NADL–F tasks are reliable in time (all coefficients above 0.63 and most above 0.80) and that there is excellent agreement in scoring among raters (all coefficients above 0.91).

After the Item analysis and Cronbach's alpha inspection, three tasks initially developed for NADL–F were discarded. It is worth briefly commenting on one of these tasks, the Price Knowledge task, in which the participant was asked to estimate the price of objects or services, spanning from common items (e.g. the cost of 1 litre of milk), to uncommon items (e.g. the cost of a round-trip from Venice to New York). This task was removed from the final version of NADL–F as it showed low consistency in the items (alpha < 0.5). There are two possible explanations for this result. One explanation is purely methodological: the low consistency in the Price Knowledge task might be a consequence of the items included in the task, and replacing the items might results in a more satisfactory consistency. The other explanation is theoretical: the low consistency is a consequence of the investigated construct (i.e., knowledge of prices of goods and services in everyday life), which is not easily captured by a single dimension. Knowledge of prices strongly depends on personal experience related to occupation and socio-cultural background. This was confirmed by the high variability in the normative data group (i.e. healthy participants). The results on this discarded task highlight the difficulties of measuring price knowledge in pathological patients, given that even healthy controls show widely varying degrees of knowledge.

The comparison between results on NADL–F performance and NADL–F interview allowed us to assess self-awareness of Financial Capacity in the participants. The overall psychometric properties of Interview were not satisfactory, especially in the test-retest ($r = 0.44$), indicating inconsistencies, in the tested sample, in reporting the own financial capacities over time. In the analysis on correlations between NADL–F tasks and NADL–F interview, significant correlations were found only between Percentages and the corresponding items of the NADL–F interview, and between Financial Judgments and the corresponding items of the interview. This pattern of results partly replicates previous findings from literature (Okonkwo et al., 2008, 2009), which suggest little awareness concerning financial capacities and serious difficulties in measuring them by means of questionnaire. Taken together, the results indicate that the NADL–F interview should not be used and suggest the importance of relying on instruments designed to directly measure financial capacity (Marson et al., 2000).

To assess the construct validity of NADL–F, we first performed a factor analysis. Two factors captured satisfactorily the NADL–F task variance. The first factor showed highest loadings in tasks requiring processing demands in basic cognitive functions such as processing speed, working memory, and attention (namely, Counting Currencies, Reading Abilities, Item Purchase, and Percentages). The second factor showed the highest loadings in all tasks requiring the retrieval of knowledge of financial concepts (Financial Concepts and Bills). These results highlight the fact that the two main aspects of financial capacity are captured by NADL–F: the performance-based capacity (related to the manipulation of information and of performing mental operations in real-life situations when using money, e.g., counting or making calculations), and knowledge-based capacity (related to knowledge of all financial concepts that an individual usually knows, such as what is a salary or a mortgage, and what home bills are commonly paid). Interestingly, Financial Judgments showed relatively low loadings on both factors. This is presumably due to the fact that making financial judgments (and detecting fraud) cannot be simply ascribed to a performance-based situation or to knowledge, but rather to another set of abilities (e.g. theory of mind Spence et al., 2004)that are not critical for other tasks. These results support the validity of NADL–F, assuming that financial abilities can be broadly divided in some activities requiring performance, and other requiring knowledge of financial issues.

The construct validity of NADL–F was further investigated by means of pairwise correlations between NADL–F tasks and several neuropsychological tests, in a mixed sample of patients and healthy controls. In this analysis a meaningful pattern of correlations emerged. Almost all NADL–F tasks correlated positively with the measure of general cognitive status (i.e., MMSE) and the performance-based cognitive tasks (Forward and Backward Digit Span, RAVLT, and Phonemic Fluency). For all these tests, in general, lower correlations were found for Counting Currencies and Reading Abilities. A significant correlation was also observed between the NADL–F tasks and the CRI-q (Nucci et al., 2012), a measure of life experiences that estimates an individual's cognitive reserve. Interestingly the CRI-q did not correlate with Counting Currencies or Item Purchase. This is probably due to the fact that the CRI-q assesses the work- socio- and cultural-related experiences of individuals. Thus, familiarities with common activities such as shopping or dealing with money are not captured by this measure of cognitive reserve. The Depression scale did not correlate with any NADL–F task, suggesting that mood had little influence on NADL–F performance. As expected, some positive correlations were also found with IADL, a functional scale that also includes some items related to financial capacity (Lawton & Brody, 1969). The Financial Judgments task again stands out from the rest of NADL–F, showing no significant correlation with any neuropsychological test. As mentioned above, this is probably due to the different construct measured by this task.

Given the relevance of numerical competence (such as reading and writing numbers, or performing mental calculations) in financial capacities (Sherod et al., 2009), we investigated the relationship between NADL–F and NADL in a sample of patients and controls. The NADL is composed of several tasks aimed at investigating several basic aspects of mathematical competence and their relation to general activities of daily living (Semenza et al., 2014). As expected, several NADL–F tasks showed significant (and relatively high) correlations with NADL tasks. Interestingly, significant correlations were not confined to the (expected) NADL–F tasks directly based on mental calculation (such as Item Purchase, or Percentages), but were also observed for the knowledge-based tasks (Financial Concepts and Bill Payments). A qualitative inspection of correlation coefficients shows that the correlation observed between NADL–F and NADL is higher than any other correlation with other neuropsychological tests. This finding seems in line with findings by Sherod et al. (2009). One explanation is that numerical competence is the cognitive ability that mostly influences financial abilities. A second possible explanation, however, is that there is another factor (e.g. a combination of knowledge and working memory abilities) that constitutes the grounding of both numerical competence and financial abilities. Interestingly, a study on traumatic brain injury patients, already highlighted the importance of numerical abilities as good predictors of recovery of financial capacities (Martin et al., 2012). To sum up, the correlations observed in the present study support the relevance of the relationship between mathematical competence and financial capacity, and suggest the need for further studies to shed light on this issue.

The effect of demographic variables on NADL–F performance in healthy controls showed a consistent effect of education: overall, as expected, as education increases performance on NADL–F increases. However, this effect was slightly different across tasks, being linear in some cases or non-linear in other. An effect of gender was shown in two tasks (Percentages and Financial Concepts). We speculate that the poorer performance in Percentage by female participants might be related to gender-related anxiety effects of mathematical tasks (Goetz, Bieg, Ludtke, Pekrun, & Hall, 2013; Maloney, Sattizahn, & Beilock, 2014) or the influence of sociocultural factors in the sample examined (composed mostly of older adults). A sociocultural explanation may also explain the poorer results of female participants in the Financial Concepts task, given that in past generations in Italy the management of financial issues was almost always a duty of male family members.

Importantly, this study provides cut-off tables for the clinical use of NADL–F. These tables are designed to be easy to use, yet employ a state-of-the-art method to take into account the effect of demographic variables in classifying the performance (Crawford & Garthwaite, 2006). To infer a decline in financial capacities, the clinician should also have premorbid measures. These, however, are rarely available and estimates of premorbid financial capacities based on questionnaires proved to be unsatisfactory (Monaco et al., 2013). Importantly, a performance below the cut-off in NADL–F indicates that the observed scores is unexpectedly low given the variable taken into account (i.e., age, education, and gender) and from this comparison the clinician can infer that a decline likely occurred. Future studies (with larger normative sample) could make these predictions even more accurate, taking into account more variables, such as job or cognitive reserve (Nucci et al., 2012).

There are, of course, some caveats to the use of NADL–F. First, the financial capacity domains included in the current version of NADL–F are those that are most relevant in the Italian sociocultural context, The materials we provide cannot be simply translated to be used in other languages and cultures: adaptation of NADL–F into other languages and for other cultures should take into account that adjustments in some items or domains might be necessary. Secondly, performance on NADL–F (as performance on any test on financial capacity) cannot provide an exhaustive picture of financial capacity but should be interpreted as the assessment of the domains that are actually considered. Financial capacity, as discussed in the introduction, is a multifaceted construct (Kershaw & Webber, 2004), and for this reason only some domains can be assessed in the limited time of clinical assessment. Clinicians should be aware of this limitation when drawing conclusions from NADL–F performance.

In summary, the NADL–F tasks are sufficiently reliable and show good validity for measuring constructs related to financial abilities and competence in daily living. Despite the relevance of financial capacities in an individual's life, so far only few instruments have been designed for their assessment (Marson & Zebley, 2001). The assessment of Financial Capacities is of particular interest in those populations at high risk of financial exploitation, such as people with AD or MCI (Griffith et al., 2003; Marson, 2013; Marson et al., 2000). To achieve this goal, NADL–F is a new tool that could help the clinician to draw specific conclusions on the financial autonomy of an individual. The present study preliminarily tested the feasibility of using the NADL–F in several clinical populations and future studies could investigate more deeply the cognitive and neural correlates of financial capacities across different neurological pathologies. The evaluation of Financial Capacities with a specific assessment tool such as NADL-F is meant to play a fundamental role in rehabilitation, allowing to tailor treatment to enhance these abilities, and to monitor these abilities over time.

To our knowledge, the NADL–F is the first instrument validated and normed in a European country, which takes into account the relevant aspects of financial capacities in this specific context. With this first validation of NADL–F for an Italian sample, and by sharing all materials and methodologies, we hope to promote further adaptation and translations to other languages and to different sociocultural contexts.

Study 7: Anatomical substrates and neurocognitive predictors of financial abilities in mild cognitive impairment

(In preparation)

7.1. INTRODUCTION

Financial Capacity is "the ability to independently manage one's financial affairs in a manner consistent with personal self-interest and values" (Widera, Steenpass, Marson, & Sudore, 2011). It may indeed be considered among the most important functional abilities of daily living related to the independence of the individual (Demakis, 2012). Several studies indicate that in pathological aging, Mild Cognitive Impairment (Griffith et al., 2003) or Alzheimer's disease (Marson et al., 2000), Financial Abilities (FA) are impaired, and that a deficit in FA is a marker of cognitive decline.

In particular, deficits in financial abilities (FA) contribute to the difficulties experienced by patients with mild cognitive impairment (MCI) in everyday life activities. Impairments in tasks tapping financial capacities such as financial conceptual knowledge, bank statement management and bill payment have, in fact, been reported in these patients (Griffith et al., 2003, 2010; Okonkwo et al., 2006; Sherod et al., 2009). Importantly, the decline of FA in MCI can give rise to legal issues connected with financial abuse and exploitation (Marson et al., 2000).

Numerical deficits in MCI may be primary or secondary to other cognitive difficulties. Griffith et al., (2003), in particular, related financial impairments to deficits in executive functions. One interesting question is thus whether financial difficulties experienced by MCIs are the result of specific regional anatomical changes. Despite the importance of FA in pathological aging, only few studies, indeed, investigated the neural correlates of these abilities (Griffith et al., 2010; Triebel et al., 2009). Of the available neuroimaging technologies, structural MRI volumetrics is a potentially useful tool to examine IADL changes in MCI because it is sensitive to atrophy in people with MCI, is correlated with cognitive function in MCI, and has generally good correspondence with AD pathology at autopsy. In their study Griffith et al., (2010) investigated MRI volumetrics of four structures suspected to play a role in financial abilities in persons with amnestic MCI: the medial prefrontal lobes, the hippocampi, the medial parietal lobe and pre-cunei, and the angular gyri. They chose these structures because these brain regions are particularly affected in MCI and AD and because of their prior association with cognitive abilities that could influence financial abilities. They found that people with MCI performed significantly below controls on their test, the financial capacity instrument (FCI), and had significantly smaller hippocampi. Among people with MCI, performance on the FCI was moderately correlated with angular gyri and pre-cunei volumes. Regression models demonstrated that angular gyrus volumes were predictive of FCI scores. Tests of mediation showed that measures of arithmetic and possibly attention partially mediated the relationship between angular gyrus volume and FCI score. In other words, impaired financial abilities in amnestic MCI correspond with volume of the angular gyri as mediated by arithmetic knowledge. These findings suggest that early neuropathology within the lateral parietal region in MCI leads to a breakdown of cognitive abilities that affect everyday financial skills.

In a previous study, Griffith et al., (2007) suggested that metabolic abnormalities of posterior cortical paralimbic regions may reflect the underlying neuropathological processes that are instrumental in the degradation of financial abilities in mild AD. Stoeckel et al., (2013) found that Mild AD patients performed significantly below comparisons on the FCI and had significantly smaller hippocampi. Among mild AD patients, FCI performance was moderately correlated with frontal (medial and dorsolateral frontal cortex) and posterior (angular gyri and pre-cunei) cortical volumes. There is accumulating evidence that prefrontal systems play an important role in management of personal finances including income and credit card use (Spinella, Yang, & Lester, 2007, 2009).

These studies thus established a connection with damage to specific areas of the brain and a generic index of financial impairment. What is still missing is the distinction between, on the one side, the neurological correlates of FA disturbances secondary to damage to more general cognitive functions, and, on the other side, the neurological underpinning of primary disturbances of FA, if any.

The hypothesis of the present study is that the atrophy of specific brain regions will correlate with specific financial tasks of the test NADL–F (Arcara, Burgio et al., submitted **Study 6**). If previously learned mathematical and financial concepts and facts are deteriorating in MCI, then age-related compensatory mechanisms and functional reorganization might increasingly be more salient, however: loss of efficiency in specific areas may result in taking over by other areas. Thus, for instance, a shift from parietal to frontal functioning, for which there is existing evidence in aging (Lövde et al., 2010) is expected, independently of whether these changes lead to effective compensation. Such functional reorganization is likely to reflect an increasing load on frontal executive functions (see Benavides-Varela et al., 2015). Parallel deterioration of linguistic and visuospatial abilities might also modulate this process. In order to investigate these neural changes, the present study will explore the pattern of association between financial abilities assessed with Numerical Activities of Daily Living Financial (NADL–F) and volumetric properties of the brain, both in patients diagnosed with MCI and in healthy controls.

7.2. METHODS

7.2.1. PARTICIPANTS

Eighty-one elderly adults were invited to undertake a comprehensive clinical, neuropsychiatric, and neuropsychological examination at the IRCCS San Camillo Hospital (Lido-Venice, Italy). After completing a full neurological and neuropsychological assessment, participants were divided in two groups according to the Petersen et al., criteria for diagnosing MCI (Petersen et al., 2001). Forty-four participants were diagnosed as having MCI, and thirty-seven were enrolled in the control group because they showed no sign of cognitive impairment. Other sources of cognitive impairment such as focal lesions were ruled out by visual inspection of MRI scans, carried out by an experienced neuro-radiologist unaware of the aims of this research project. All participants were right-handed and none of them had a history of psychiatric disorder, drugs or alcohol abuse. There were no significant differences between MCI patients (M =10.96 y, *SD* = 4.57) and the control group (M = 12.47 y, *SD* = 4.42) in scholastic attainment estimated in years of education (p >. 05). Significant differences between the two groups were instead found in age $t(79) = -3.4$, $p < .001$, $d = -.76$ (controls M = 68.53 y, *SD* = 10.59; MCI M = 75.27, *SD* = 7.14) see **Table 7.1**.

Table 7.1 | Summary of demographical variables and NADL–F scores of all participants.

	Df	t	Cohen's *d*	*p*	*p*−FDR	*p*−Bonferroni	Mean Controls (*SD*)	Mean MCI (*SD*)
Age	79	-3.4	-0.76	0.001	0.002	0.009	68.53 (10.59)	75.27 (7.14)
Education	79	1.5	0.34	0.136	0.136	1	12.47 (4.42)	10.96 (4.57)
Counting Currencies	79	2.4	0.53	0.021	0.027	0.188	4.69 (0.58)	4.22 (1.08)
Reading Abilities	79	3.2	0.72	0.002	0.003	0.016	6.47 (0.65)	5.8 (1.1)
Item Purchase	79	3.4	0.76	0.001	0.002	0.009	13.06 (1.24)	11.62 (2.27)
Percentages	79	4.4	0.98	0.001	0.001	0.001	7.25 (1.4)	5.4 (2.19)
Financial Concepts	79	5	1.1	0.001	0.001	0.001	9.5 (1.8)	7.07 (2.43)
Bills Payment	79	5.3	1.2	0.001	0.001	0.001	5.14 (0.87)	3.76 (1.37)
Financial Judgements	79	2.2	0.49	0.03	0.034	0.269	5.69 (0.52)	5.18 (1.32)

As a consequence, these two variables were included as covariates in all analyses. Written informed consent was obtained from all participants after the nature of the study was fully explained. The study was approved by the Institutional Review Board of the IRCCS Fondazione Ospedale San Camillo (Venice, Italy).

7.2.2. Measures

Cognitive assessment

All participants were recruited and assessed at the IRCCS San Camillo, Lido of Venice, Italy. They were all tested individually. Testing was administered by trained neuropsychologist. Every participant took part into two sessions lasting about one hour each. The first session involved the neuropsychological assessment as part of their clinical evaluation. This battery evaluates the general cognitive functioning and the cognitive domains frequently affected by dementia including measures of attention, executive functions, reasoning, language, memory, and visuospatial abilities.

The aim was to obtain cognitive profiles that could be clinically informative and sensitive to the impact of early stage neurodegeneration.

During the second session the participant underwent the NADL–F battery plus the interviews.

Financial Abilities Assessment

A new tool of Financial Abilities (FA) called Numerical Activities of Daily Living – Financial (NADL–F, Arcara, Burgio et al., submitted –**Study 6**) was administered to all participants. The battery was specifically designed for the investigation of FA and it has been standardized for the Italian population.

The final version of NADL–F test was composed of seven tasks[3] assessing different aspects of financial capacity. All tasks included several items, designed to be of increasing difficulty when possible.

[3] The initial version of NADL−F comprised a total of ten tasks. Three tasks: Price Knowledge, Guided Purchase, and Financial Planning were not included in the final version, since they showed unsatisfactory psychometric properties, especially because of the internal consistency of items. For this reason, these tasks are not further analysed in the manuscript.

Task 1) Counting Currencies

In this task the participant was asked to count given amounts of currencies (replication of real euro banknotes or coins) or to select a specific quantity of money from a given amount. This task aimed to evaluate if the participant is familiar with the euro currency and was able to perform simple mental calculations, analogous to those involved in simple cash transactions but in a simplified setting.

Task 2) Reading Abilities

In this task the participant was asked to read, transcode, and manipulate written information (mainly written numbers) presented in ecological contexts, such as replication of bills or of checks. The aim of this task is to evaluate if the participant is able to deal with written information about money in everyday life situations.

Task 3) Item Purchase

In this task the participant was asked to simulate some purchases in a shop, buying one or more items. They were asked to pay the correct amount and to check if the correct change is given after the payment. The aim of this task was to evaluate the ability of the participant to deal with operations (calculations, keeping in mind the relevant information) that are necessary to make cash transactions during shopping in real life.

Task 4) Percentages

This task consisted of a series of questions on percentages, presented as real life concrete examples. The aim of this task was to investigate if the participant is able to perform the mental calculations needed in percentages.

Task 5) Financial Concepts

In this task the participant was asked to define a series of concepts related to financial capacity (e.g. salary, IBAN). The aim of this task was to investigate the participant's knowledge of financial concepts that are more relevant to the Italian cultural context.

Task 6) Bill Payments

This task consisted of different items, all related to the practical and conceptual ability of dealing with home bills (e.g., telephone, electric current). It aimed to specifically evaluate managing bills, which is one of the most relevant domains demonstrating financial independence in the Italian sociocultural context.

Task 7) Financial Judgments

In this task the participant was presented with a series of hypothetical scenarios, in which an agent performs a financial choice. Only a third of the scenarios contributed to the final score, whereas the others acted as fillers. In the relevant scenarios the main character was often the victim of a fraud (the most common types of fraud were included). The aim of this task was mainly to evaluate whether the participant was able to make meaningful financial judgments and detect fraudulent behaviours. The filler scenarios were included to distract the participants from the aim of the task.

The NADL–F Interview

This interview was designed to investigate the awareness of an individual's financial capacity. The interview was composed of several questions reflecting the same aspects evaluated in the NADL–F tasks. For example, for the Counting Currencies task the participant was presented with a series of sentences such as "are you able to count coins or to give the correct change", "Do you recognize coins?", etc. In the interview there was no correct or wrong answer: participants are asked to rate if they were capable of performing the described activity autonomously, capable with external aid, or if they were not capable (similary to Wadley et al., 2003).

7.2.3. Statistical analysis of behavioural data

Non-parametric Wilcoxon rank-sum tests were used to assess continuous variables, including the clinical, demographic, and performance scores in the NADL–F battery. In an initial analysis, the scores of the two groups in the three sub-sections of the NADL were compared setting Bonferroni's correction for multiple comparisons (alpha = .01). In a second analysis, each domain of the Informal and Formal assessments was compared between groups, adjusting the significance level according to the number of comparisons carried out within each sub-section (alpha = .008). Additionally, given that the two groups differed in age (see Section 7.2.1), a further Pearson's correlation analysis was carried out to evaluate the association between age and scores on each sub-test and domain of the NADL–F battery.

7.2.4. MRI acquisition, pre-processing and analysis

Three-dimensional (3D) T1-weighted MR images were acquired using a 1.5 T Philips Achieva MRI system with a Turbo Field Echo sequence. Voxel dimensions were 1.1 × 1.1 × .6 mm and the field of view was 250 mm with a matrix size of 256 × 256 × 124. In addition, a T2-weighted axial scan and a coronal fluid attenuated inversion recovery (FLAIR) scan were also acquired to detect the presence of significant vascular pathology or micro bleeds, which might either be not compatible with the diagnosis of MCI prodromal to AD or induce a suboptimal segmentation of the T1-weighted images. A number of pre-processing steps were followed to obtain the gray matter (GM) segments from the 3D T1-weighted structural scan before carrying out statistical analyses using SPM 8 (Welcome Trust Centre for Neuroimaging, UCL, London, UK). To correct for global differences in brain shape, structural images were warped to a standard stereotactic space and segmented to extract maps of GM using the default segmentation procedure available in SPM 8 (Ashburner & Friston, 2005). Modulated-normalized GM images were then smoothed with an 8 mm FWHM Gaussian kernel to reduce variability between participants. Smoothed-modulated-normalized segments were entered into voxel-based multiple regression analyses to investigate linear correlations between GM volumes and participants' scores on each sub-test of the NADL–F battery. Age, years of education, and total intracranial volume values were included as covariates in the regression. Height threshold was set at $p < .001$ (uncorrected) for all analyses. Only cluster corrected areas (FWE) with a significance level of $p \leq .05$ and at least 1000 voxels are reported. Anatomical regions were identified using the Talairach Daemon Client (Lancaster et al., 2000), following conversion of the Montreal Neurological Institute coordinates extracted from the SPM output into Talairach coordinates using the Matlab function mni2tal (http://imaging.mrccbu.cam.ac.uk/imaging/MniTalairach).

7.3. RESULTS

7.3.1. BEHAVIOURAL RESULTS

A summary of the performance of the two groups on the NADL–F sub-sections and their corresponding domains is presented in **Figure 7.1** and **Figure 7.2**. The first set of analyses comparing the scores of the two groups in the seven NADL–F domains showed significant differences between the groups in all the domains of NADL–F battery except Counting Currencies and Financial Judgements (see **Table 7.1**). Additionally, there was no correlation between age and the participants' scores on the NADL–F 's sub-tests and domains.

Figure 7.1 | Summary of the performance on NADL–F tasks of the two groups.

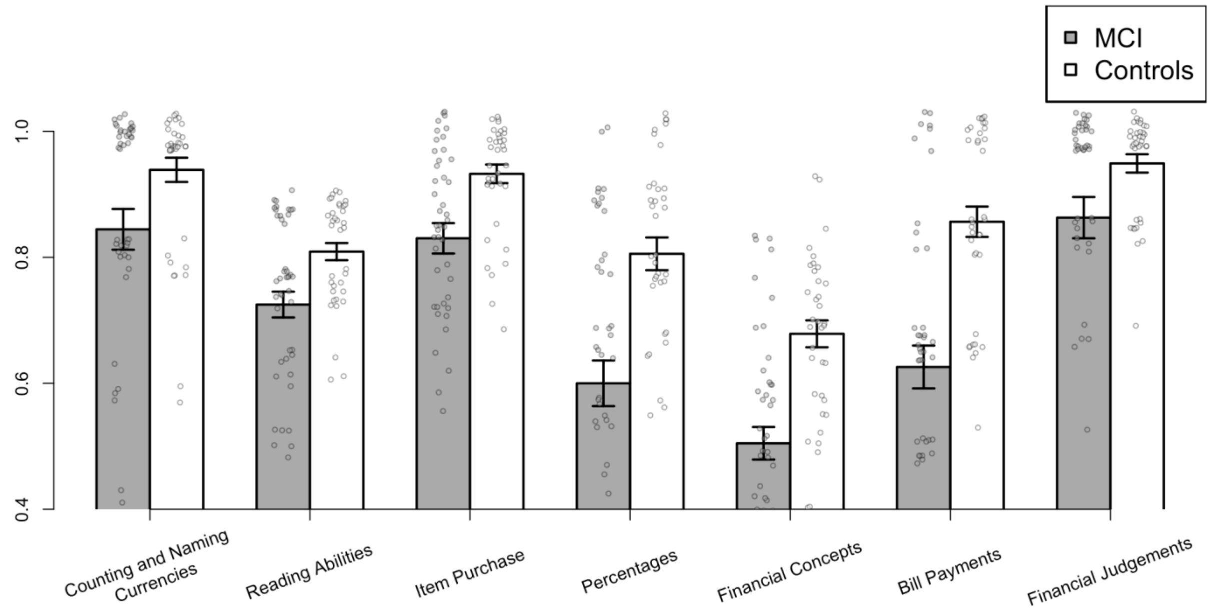
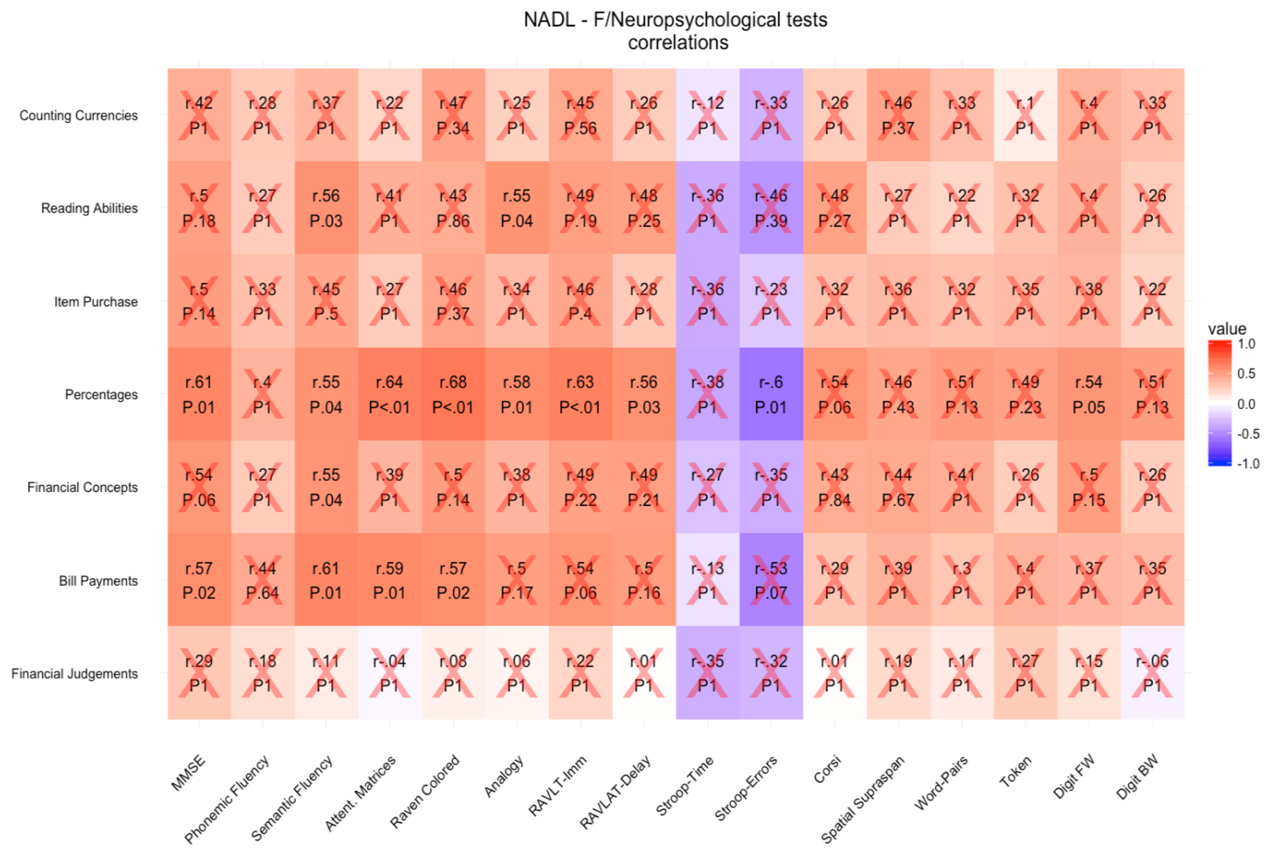


Figure 7.2 | Correlations between the Performance on NADL–F domains and neuropsychological tests of Participants with MCI (Bonferroni).



7.3.2. CORRELATIONS BETWEEN NADL–F DOMAINS AND COGNITIVE DOMAINS IN MCI

In the second set of analyses we compared the scores of the group of MCI patients in the seven NADL–F domains with the scores of the neuropsychological tests (see Supplementary Material 7).

The highest correlations were observed for the following cognitive tests: MMSE (assessing **General Cognitive functioning**), Semantic Fluency **(Language)**, Attentive Matrices **(Executive Functions and Attention)**, Raven Progressive Matrices **(Abstract Reasoning)**, Similarities **(Abstract Reasoning)**, Rey Complex Figure-Immediate **(Visuospatial Abilities)**, Rey Complex Figure-Delayed recall **(Long-term Memory)**, Stroop Errors **(Executive Functions and Attention)**, Digit Span FW **(Short-Term Memory)**. As the performance on NADL–F subtests increases, the performance in these cognitive tests increases as well, except for Stroop Errors test, which shows a negative correlation with NADL–F subtests. The NADL–F subtests showed no significant correlation with the other neuropsychological tests, indicating that Phonemic Fluency, Stroop Time, Spatial span and Supra-span, Word-Pairs, Token Test and BW Digit Span have little influence on NADL–F performance. To summarize, Language, Executive Functions and Attention, Abstract Reasoning, Visuospatial Abilities and Memory are the cognitive functions that mostly influence financial abilities supporting the multidimensional nature of the construct of financial capacity.

Table 7.2 | Correlations between NADL−F tasks and other neuropsychological tests.

	MMSE	Phonemic Fluency	Semantic Fluency	Attentive Matrices	Raven Colored	Analogy	RAVLT Immage	RAVLAT Delay	Stroop Time	Stroop Errors	Corsi	Spatial Supraspan	Word Pairs	Token	Digit FW	Digit BW
Counting Currencies	0.42	0.28	0.37	0.22	0.47	0.25	0.45	0.26	−0.12	−0.33	0.26	0.46	0.33	0.10	0.40	0.33
Reading Abilities	0.50	0.27	**0.56***	0.41	0.43	**0.55***	0.49	0.48	−0.36	−0.46	0.48	0.27	0.22	0.32	0.40	0.26
Item Purchase	0.50	0.33	0.45	0.27	0.46	0.34	0.46	0.28	−0.36	−0.23	0.32	0.36	0.32	0.35	0.38	0.22
Percentages	**0.61***	0.40	**0.55***	**0.64***	**0.68***	**0.58***	**0.63***	**0.56***	−0.38	**−0.6***	0.54	0.46	0.51	0.49	**0.54***	0.51
Financial Concepts	0.54	0.27	**0.55***	0.39	0.50	0.38	0.49	0.49	−0.27	−0.35	0.43	0.44	0.41	0.26	0.50	0.26
Bill Payments	**0.57***	0.44	**0.61***	**0.59***	**0.57***	0.50	0.54	0.50	−0.13	−0.53	0.29	0.39	0.30	0.40	0.37	0.35
Financial Judgements	0.29	0.18	0.11	−0.04	0.08	0.06	0.22	0.01	−0.35	−0.32	0.01	0.19	0.11	0.27	0.15	−0.06

This table reports the r values of Pearson correlations between NADL−F task scores and other neuropsychological test scores. Stars (*) denotes significant results after Bonferroni correction for multiple comparisons.

7.4. VBM RESULTS

Voxel-based regression models

The NADL–F sub-tests and domains that showed significant between-group differences in the behavioural analyses were entered into separate regression models to evaluate the GM volume correlations with the tests. *Counting Currencies* scores showed significant positive correlations with GM volume in the Right Uncus, Left Para-hippocampal Gyrus, Amygdala and Hypothalamus in the MCI group. Total scores of *Item Purchase* were significantly associated with GM volume values in the Left Fusiform Gyrus, Left Parahippocampal Gyrus, Left Superior Temporal Gyrus, Right Caudate Head, Left Caudate Body, Left Lentiform Nucleus, Right Anterior Cingulate, Left Cingulate Gyrus areas in the MCI group. Similarly, *Percentages and Financial Concepts* tasks showed significant positive correlations with GM volume in Left Mammillary Body, Left Thalamus, Medial Dorsal Nucleus, Right Caudate Head and Left Middle Temporal Gyrus, Left Fusiform Gyrus, Left Cingulate Gyrus, Left Thalamus, Ventral Anterior Nucleus respectively. *Bill Payments and Financial Judgments* also correlated positively with Right Caudate Body and Head, Left Lentiform Nucleus and Left Uncus, Amygdala, Left Fusiform Gyrus, Left Superior Temporal Gyrus respectively (see **Figure 7.3** and **Figure 7.4**). There were no significant correlations in other sub-tests and domains.

Significant positive correlations between scores on *Percentages* (Cerebellum, Posterior Lobe), *Financial Concepts* (Left Cuneus, Left and Right Middle Temporal Gyrus, Posterior and Anterior Lobe, Left and Right Medial Frontal Gyrus), *Financial Judgments* (Right Middle Temporal Gyrus, Right Inferior Frontal Gyrus, Right Precentral Gyrus, Left Uncus, Left Lentiform Nucleus, Putamen, Left Inferior Frontal Gyrus) and brain volumes (GM) were found in the control group. **Table 7.3** (**Table 7.4** & **Table 7.5**) shows a summary of the findings.

Table 7.3 | Correlations between GM volume and NADL–F scores.

	Group	Number of voxels per cluster	Cluster level *p* value (uncorrected)	FWE corrected *p* value at cluster level	*Z* Value at local maximum	Talairach coordinates			Brain region (Brodmann's area)
						x	y	z	
Counting Currencies	MCI	9565	< 0.001	0.018	4.24	32	−7	−25	Right Uncus (BA 28)
	MCI				3.96	−30	−7	−20	Left Parahippocampal Gyrus, Amygdala
	MCI				3.84	0	−3	−12	Hypothalamus
Item Purchase	MCI	3557	< 0.001	< 0.001	4.73	−34	−11	−22	Left Fusiform Gyrus (BA 20)
	MCI				4.50	−36	−22	−17	Left Parahippocampal Gyrus (BA 36)
	MCI				4.49	−39	13	−28	Left Superior Temporal Gyrus (BA 38)
	MCI	2861	< 0.001	< 0.001	4.35	−6	0	0	Left Lentiform Nucleus
	MCI				3.69	6	15	−4	Right Caudate, Caudate Head
	MCI				3.56	−12	12	8	Left Caudate, Caudate Body
	MCI	1514	0.001	0.020	3.74	6	24	18	Right Anterior Cingulate (BA 24)
	MCI				3.43	−8	−22	32	Left Cingulate Gyrus (BA 23)
	MCI				3.29	−14	−13	37	Left Cingulate Gyrus (BA 24)
Percentages	Controls	2171	< 0.001	0.001	3.79	12	−69	−14	Right Cerebellum Posterior Lobe Declive
	Controls				3.43	−20	−68	−18	Left Cerebellum Posterior Lobe Declive
	Controls				3.30	18	−69	−19	Right Cerebellum Posterior Lobe Declive
	MCI	1971	< 0.001	0.005	4.28	−2	−12	−4	Left Brainstem Midbrain, Mammillary Body
	MCI				3.58	−2	−13	10	Left Thalamus, Medial Dorsal Nucleus
	MCI				3.13	6	8	1	Right Caudate, Caudate Head

Table 7.4 | Correlations between GM volume and NADL–F scores *(continue).*

	Group	Number of voxels per cluster	Cluster level *p* value (uncorrected)	FWE corrected *p* value at cluster level	*Z* Value at local maximum	Talairach coordinates x	y	z	Brain region (Brodmann's area)
Financial Concepts	Controls	1994	< 0.001	0.001	4.28	−6	−84	6	Left Cuneus (BA 17)
	Controls				4.06	−2	−88	17	Left Cuneus (BA 18)
	Controls				3.88	−3	−80	23	Left Cuneus (BA 18)
	Controls	5575	< 0.001	< 0.001	4.19	−55	−44	−10	Left Middle Temporal Gyrus (BA 20)
	Controls				3.76	−50	−60	−29	Left Cerebellum Posterior Lobe Tuber
	Controls				3.70	−32	−71	−13	Left Fusiform Gyrus (BA 19)
	Controls	1396	< 0.001	0.010	3.89	−6	−46	−25	Left Cerebellum Anterior Lobe
	Controls				3.78	2	−42	−28	Right Cerebellum Anterior Lobe
	Controls				3.04	−10	−37	−39	Left Cerebellum Posterior Lobe Cerebellar Tonsil
	Controls	1368	< 0.001	0.011	3.72	55	−49	−8	Right Middle Temporal Gyrus (BA 37)
	Controls				3.57	46	−65	−22	Right Cerebellum Posterior Lobe Declive
	Controls				3.51	34	−69	−14	Right Cerebellum Posterior Lobe Declive
	Controls	1655	< 0.001	0.004	3.46	−6	38	−12	Left Medial Frontal Gyrus (BA 11)
	Controls				3.44	3	51	0	Right Medial Frontal Gyrus (BA 10)
	Controls				3.27	3	43	−10	Right Medial Frontal Gyrus (BA 11)
	MCI	9958	< 0.001	0.014	4.38	−57	−3	−20	Left Middle Temporal Gyrus (BA 21)
	MCI				3.76	−57	−5	−27	Left Fusiform Gyrus (BA 20)
	MCI				3.43	−48	−20	−21	Left Fusiform Gyrus (BA 20)
	MCI	8377	< 0.001	0.036	3.68	−12	−15	41	Left Cingulate Gyrus (BA 24)
	MCI				3.63	−15	−8	14	Left Thalamus, Ventral Anterior Nucleus
	MCI					−3	−1	31	Left Cingulate Gyrus (BA 24)

Table 7.5 | Correlations between GM volume and NADL–F scores *(continue).*

	Group	Number of voxels per cluster	Cluster level *p* value (uncorrected)	FWE corrected *p* value at cluster level	*Z* Value at local maximum	Talairach coordinates			Brain region
						x	y	z	(Brodmann's area)
Bill Payments	MCI	1973	0.000	0.005	3.74	18	−3	20	Right Caudate, Caudate Body
	MCI				3.61	9	2	4	Right Caudate, Caudate Head
	MCI				3.58	−8	3	−3	Left Lentiform Nucleus
Financial Judgments	Controls	10194	0.000	0.004	3.57	57	−10	−3	Right Middle Temporal Gyrus (BA 21)
	Controls				3.52	28	18	−19	Right Inferior Frontal Gyrus (BA 47)
	Controls				3.49	48	3	11	Right Precentral Gyrus (BA 44)
	Controls	8348	0.000	0.013	3.13	−24	8	−21	Left Uncus (BA 28)
	Controls				3.06	−15	8	−2	Left Lentiform Nucleus, Putamen
	Controls				2.91	−30	19	−3	Left Inferior Frontal Gyrus (BA 47)
	MCI	2838	0.000	0.001	4.46	−24	−3	−25	Left Uncus, Amygdala
	MCI				4.27	−55	−25	−26	Left Fusiform Gyrus (BA 20)
	MCI				3.98	−50	8	−19	Left Superior Temporal Gyrus (BA 38)

Figure 7.3 | Representative regions evidencing significant differences in MCI patients and healthy controls on specific NADL–F subtests.

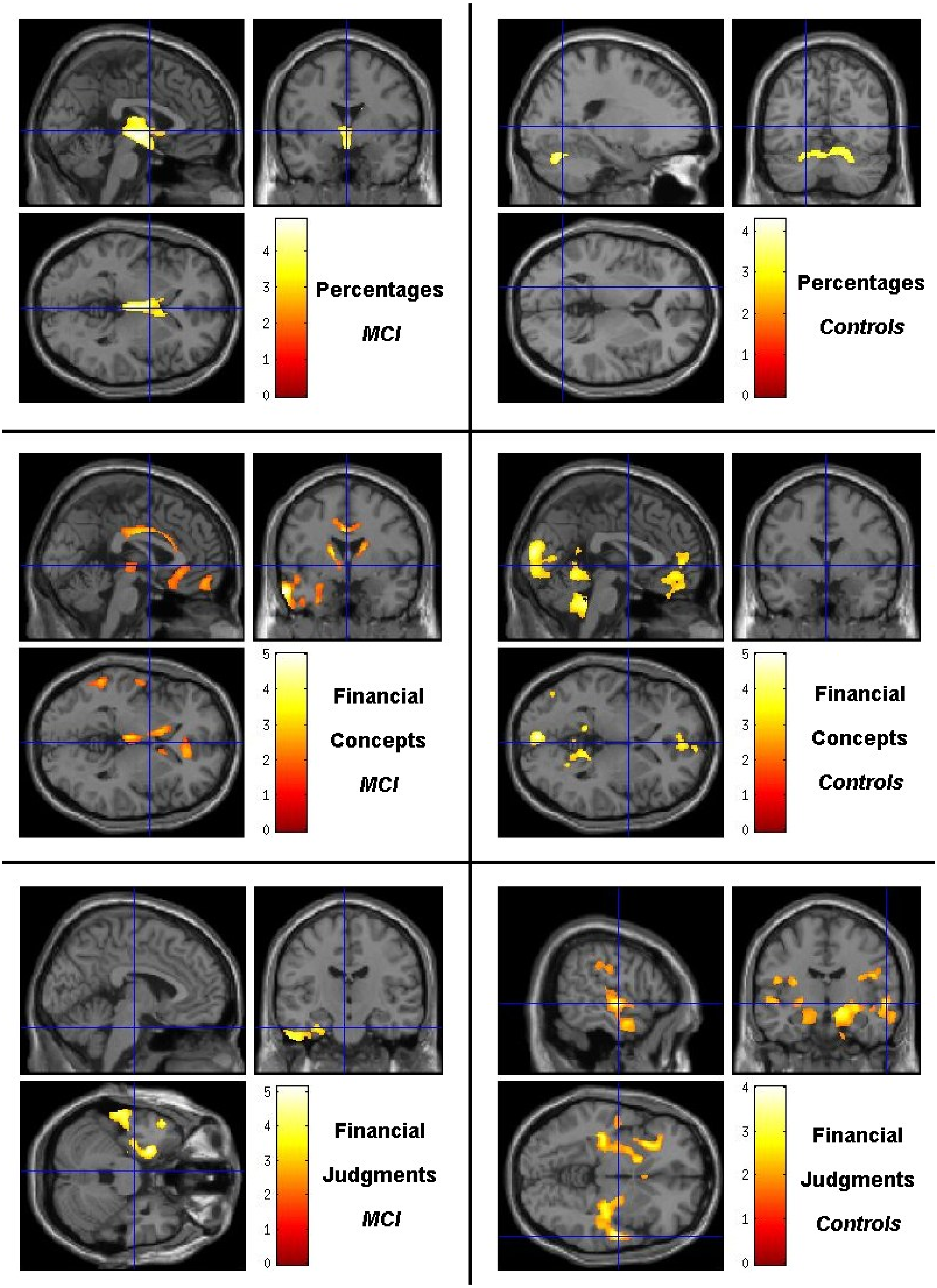
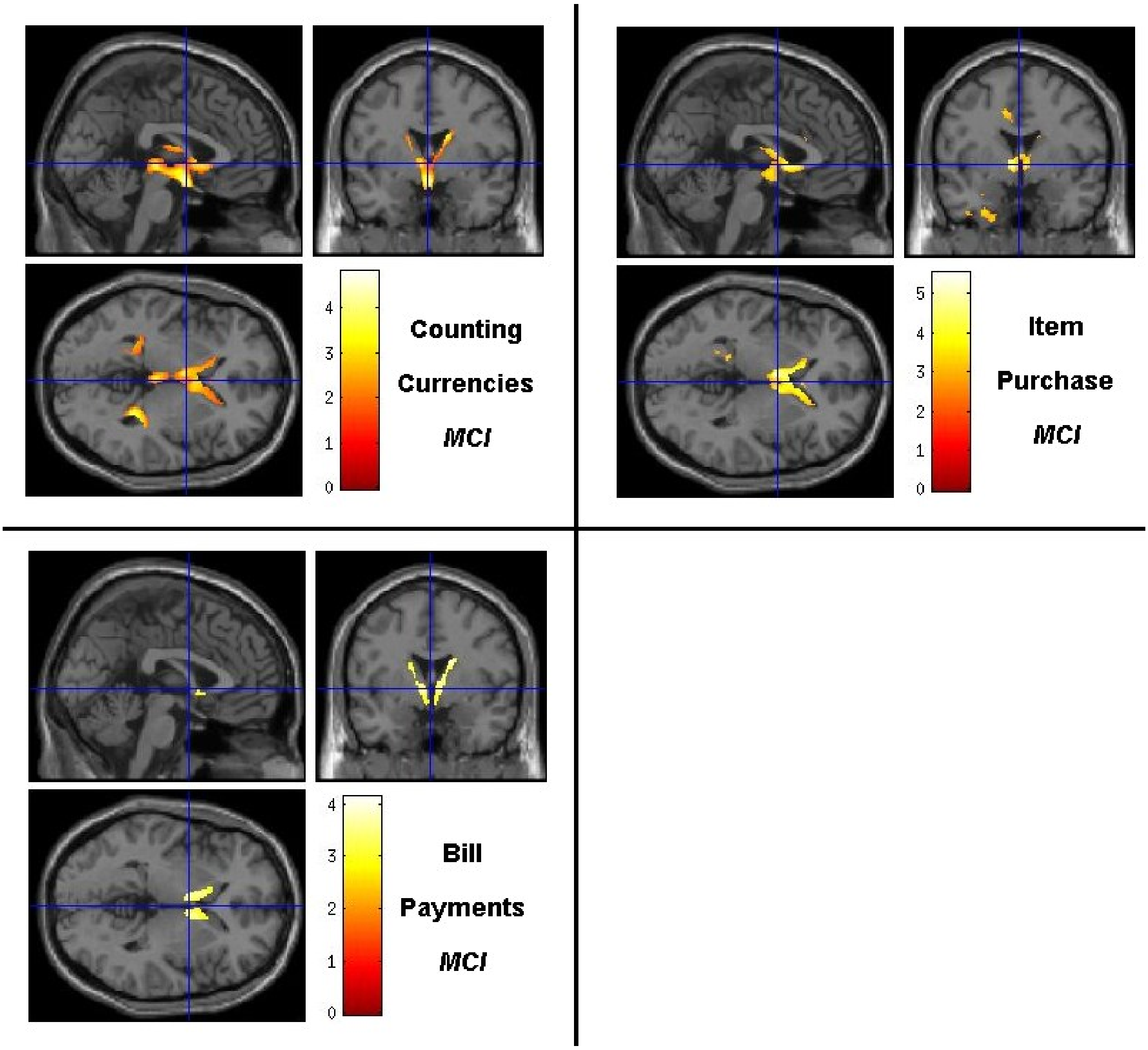


Figure 7.4 | Representative regions evidencing significant differences in MCI patients on specific NADL–F subtests.



No significant correlations between NADL–F scores and brain volumes (GM) were found in the control group in these domains.

7.5. Discussion

These results are preliminary and require further statistical analysis and investigation. Overall, a surprising and potentially novel result is, in MCI with respect to normals, a major involvement of limbic structures (rather than neocortical structures) in financial tasks. It is hard, at present time, to provide a full and detailed interpretation of such result. It looks as if, when cortical areas deteriorate and cognitive decline takes over, emotional aspects emerge in front of tasks pertaining to a domain where desire normally plays a major role. As a consequence, the main differences in activation concern limbic structures including subcortical ones. Along these lines it is intriguing to observe that the involvement of limbic structures seems to emerge more conspicuously for tasks, like counting currencies and shopping, that have a rewarding connotation, rather than in tasks as bill payments and financial judgements, where no such direct pleasant connotation is there.

If the above interpretation is correct, then one can envisage the following scenario. MCI patients, when confronted with financial matters, are at risk of behaving less rationally and on the spur of their immediate appetite, dictated by the prevailing activation of limbic structures. This may result in non-mindful, unwise decisions and higher gullibility, ultimately leading to a disadvantageous course of action.

GENERAL DISCUSSION AND CONCLUSION

The series of studies reported in this thesis represent an advancement in clinical assessment and in the neuropsychology of math in several respects:

1) New assessment tools, NADL, NADL–F and NADL–Children have been built and validated.

2) NADL, a new instrument for the assessment of mathematical abilities includes, for the first time, numerical activities of daily living. It relates one's ability in dealing with such activities to basic math abilities. It also shows (see the study on neurofibromatosis) how patients with basic defects in math cognition may still be functional in daily life. It has been made available on-line for everybody who wants to use it.

3) These instruments have been used to evidence specific profiles of impairment in different neurological conditions (MCI, Neurofibromatosis type 1 and right hemisphere focal lesions) (See **Table D.1**). This is an on-going enterprise: further populations, not reported about in the present thesis have been the object of separate investigations.

4) Knowledge about the anatomical correlates of math abilities has been improved for some pathological conditions and interesting data have been found on the evolution of these correlates in progressive diseases and aging.

5) NADL-Children proved to be able to predict, before primary school is attended, mathematical performance and learning after the first year on the basis of the numerical exposure they enjoyed at home.

6) The role of the right hemisphere, traditionally believed to be confined to spatial components of mathematical cognition, was shown to extend to non-spatial components, thus confirming recent studies made with TMS, neuroimaging and awake surgery (see Salillas & Semenza, 2014, for a review of these data).

7) An instrument for the assessment of financial abilities, NADL–F has been made available and ready to use in the Italian context. It can be easily adapted for use at least in the Euro areas. It

can be used for clinical purposes but also for forensic purposes. It will also be made available on-line. NADL–F, still ongoing studies show, cannot be substituted by less specific and less powerful tools. It will be interesting to see (as indeed preliminary studies seem to show) that its outcome not only cannot be predicted on the basis of more generic tests of intelligence, but even by NADL. Some people may have serious mathematical problems and yet be essentially still able to deal with some aspects of their finances. This would be of pivotal interest in forensic medicine.

In conclusion, as it has become clear, however, all this work calls for further work, not all of which of a scientific nature. The clinical assessment of math cognition is, unfortunately, in fact, hardly administered routinely in clinical institutions and in rehabilitation programs. Rehabilitation programs, in fact, almost never include rehabilitation of math, thus ignoring the importance of such ability in everyday life. The chance of a brain damaged patient to become again a numerate citizen, an important feature in modern life, is thus very unlikely.

This consideration ends this thesis on a sad note. But denying these facts would make things worse. Disseminating these results may encourage to make up for this social shortcoming.

Table D.1 | Specific pattern of errors found in NADL and NADL–F domains found in patients with different pathologies.

	NADL		NADL–F
	INFORMAL	FORMAL	
MILD COGNITIVE IMPAIRMENT	Time estimation Money usage	Number Comprehension Transcoding Logic and Principles Written Operations	Counting Currencies Reading Abilities Item Purchase Percentages Financial Concepts Bill Payments Financial Judgements
NEUROFIBROMATOSIS TYPE 1	✓	Written Operations Logic and Principles Number comprehension	—
RIGHT-HEMISPHERE DAMAGED PATIENTS	General knowledge of numerical facts in everyday life Time estimation Money usage	Number comprehension Transcoding Written operations	—

ACKNOWLEDGMENTS

I wish to thank my research group Silvia Benavides-Varela, Giorgio Arcara, Francesca Meneghello and Carlo Semenza to be my guidance during the present research, Cristina Pilosio for helping during the recruitment of participants, Roberta Toffano for helping in data collection and Micaela Mitolo for the guidance on the VBM analysis.

I wish also to thank the neuropsychological unit of IRCCS San Camillo Hospital and all the people who collaborated during the present research, as well as the patients and participants who took part in the study.

Finally, I wish to thank my family, especially my father who has made this possible.

This research has been supported by the Italian Ministry of Health (RF-2009-1530973) and by "Progetto strategico NEURAT (STPD11B8HM)" from the University of Padua to C.S.

LIST OF TABLES

LIST OF FIGURES

REFERENCES

Acosta, M. T., Gioia, G. A., & Silva, A. J. (2006). Neurofibromatosis type 1: New insights into neurocognitive issues. *Current Neurology and Neuroscience Reports*, *6*(2), 136–143. https://doi.org/10.1007/s11910-996-0036-5

Anders, Y., Rossbach, H. G., Weinert, S., Ebert, S., Kuger, S., Lehrl, S., & von Maurice, J. (2012). Home and preschool learning environments and their relations to the development of early numeracy skills. *Early Childhood Research Quarterly*, *27*(2), 231–244. https://doi.org/10.1016/j.ecresq.2011.08.003

Anderson, A. G. (1998). Parents as partners: Supporting children's mathematics learning prior to school. *Teaching Children Mathematics*, *4*(6), 331–337.

Anderson, J. R. (1993). *Rules of the Mind*. *American Psychologist*. Hillsdale, NJ: Routledge. https://doi.org/10.4324/9781315806938

Andres, M., Pelgrims, B., Michaux, N., Olivier, E., & Pesenti, M. (2011). Role of distinct parietal areas in arithmetic: An fMRI-guided TMS study. *NeuroImage*, *54*(4), 3048–3056. https://doi.org/10.1016/j.neuroimage.2010.11.009

Andres, M., Seron, X., & Olivier, E. (2007). Contribution of hand motor circuits to counting. *Journal of Cognitive Neuroscience*, *19*(4), 563–76. https://doi.org/10.1162/jocn.2007.19.4.563

Arcara, G., & Bambini, V. (2016). A Test for the Assessment of Pragmatic Abilities and Cognitive Substrates (APACS): Normative Data and Psychometric Properties. *Frontiers in Psychology*, *7*, 70. https://doi.org/10.3389/fpsyg.2016.00070

Ardila, a, & Rosselli, M. (1994). Spatial acalculia. *The International Journal of Neuroscience*, *78*(3–4), 177–184. https://doi.org/10.3109/00207459408986056

Arsalidou, M., & Taylor, M. J. (2011). Is 2+2=4? Meta-analyses of brain areas needed for numbers and calculations. *NeuroImage*, *54*(3), 2382–2393. https://doi.org/10.1016/j.neuroimage.2010.10.009

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, *26*(3), 839–851. https://doi.org/10.1016/j.neuroimage.2005.02.018

Ashcraft, M. H., & Battaglia, J. (1978). Cognitive arithmetic: Evidence for retrieval and decision processes in mental addition. *Journal of Experimental Psychology: Human Learning & Memory*, *4*(5), 527–538. https://doi.org/10.1037/0278-7393.4.5.527

Aunola, K., Leskinen, E., Lerkkanen, M.-K., & Nurmi, J.-E. (2004). Developmental Dynamics of Math Performance from Preschool to Grade 2. *Journal of Educational Psychology*, *96*(4), 699–713. https://doi.org/10.1037/0022-0663.96.4.699

Barrouillet, P., Camos, V., Perruchet, P., & Seron, X. (2004). ADAPT: a developmental, asemantic, and procedural model for transcoding from verbal to arabic numerals. *Psychological Review*, *111*(2), 368–394. https://doi.org/10.1037/0033-295X.111.2.368

Basso, A., Burgio, F., & Caporali, A. (2000). Acalculia, Aphasia and Spatial Disorders in Left and Right Brain-Damaged Patients. *Cortex*, *36*(2), 265–280. https://doi.org/10.1016/S0010-9452(08)70528-8

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., & Dronkers, N. F. (2003). Voxel-based lesion–symptom mapping. *Nature Neuroscience*, *6*(5), 448–450. https://doi.org/10.1038/nn1050

Benavides-Varela, S., Burgio, F., Meneghello, F., De Marco, M., Arcara, G., Rigon, J., … Semenza, C. (2015). Anatomical substrates and neurocognitive predictors of daily numerical abilities in mild cognitive impairment. *Cortex*, *71*, 58–67. https://doi.org/10.1016/j.cortex.2015.05.031

Benavides-Varela, S., Butterworth, B., Burgio, F., Arcara, G., Lucangeli, D., & Semenza, C. (2016). Numerical Activities and Information Learned at Home Link to the Exact Numeracy Skills in 5–6 Years-Old Children. *Frontiers in Psychology*, *7*, 94. https://doi.org/10.3389/fpsyg.2016.00094

Benavides-Varela, S., Passarini, L., Butterworth, B., Rolma, G., Burgio, F., Pitteri, M., … Semenza, C. (2016). Zero in the brain: A voxel-based lesion-symptom mapping study in right hemisphere damaged patients. *Cortex*, *77*, 38–53. https://doi.org/10.1016/j.cortex.2016.01.011

Benavides-Varela, S., Pitteri, M., Priftis, K., Passarini, L., Meneghello, F., & Semenza, C. (2014). Right-hemisphere (spatial?) acalculia and the influence of neglect. *Frontiers in Human Neuroscience*, *8*(August), 644. https://doi.org/10.3389/fnhum.2014.00644

Benke, T., Delazer, M., Bartha, L., & Auer, A. (2003). Basal ganglia lesions and the theory of fronto-subcortical loops: neuropsychological findings in two patients with left caudate lesions. *Neurocase*, *9*(1), 70–85. https://doi.org/10.1076/neur.9.1.70.14374

Berkowitz, T., Schaeffer, M. W., Maloney, E. A., Peterson, L., Gregor, C., Levine, S. C., & Beilock, S. L. (2015). Math at home adds up to achievement in school. *Science*, *350*(6257), 196–198. https://doi.org/10.1126/science.aac7427

Berteletti, I., Lucangeli, D., Piazza, M., Dehaene, S., & Zorzi, M. (2010). Numerical estimation in preschoolers. *Developmental Psychology*, *46*(2), 545–51. https://doi.org/10.1037/a0017887

Bertella, L., Girelli, L., Grugni, G., Marchi, S., Molinari, E., & Semenza, C. (2005). Mathematical skills in Prader-Willi syndrome. *Journal of Intellectual Disability Research*, *49*(2), 159–169. https://doi.org/10.1111/j.1365-2788.2004.00634.x

Billingsley, R. L., Jackson, E. F., Slopis, J. M., Swank, P. R., Mahankali, S., & Moore, B. D. (2004). Functional MRI of visual-spatial processing in neurofibromatosis, type I. *Neuropsychologia*, *42*(3), 395–404. https://doi.org/10.1016/j.neuropsychologia.2003.07.008

Blevins-Knabe, B., & Musun-Miller, L. (1996). Number use at home by children and their parents and its relationship to early mathematical performance. *Early Development and Parenting*, *5*(October 1995), 35–45. https://doi.org/10.1002/(SICI)1099-0917(199603)5:1<35::AID-EDP113>3.0.CO;2-0

Blevins- Knabe, B., Austin, A. B., Musun, L., Eddy, A., & Jones, R. M. (2000). Family Home Care Providers' and Parents' Beliefs and Practices Concerning Mathematics with Young Children †. *Early Child Development and Care*, *165*(1), 41–58. https://doi.org/10.1080/0300443001650104

Booth, J. L., & Siegler, R. S. (2006). Developmental and individual differences in pure numerical estimation. *Developmental Psychology*, *42*(1), 189–201. https://doi.org/10.1037/0012-1649.41.6.189

Booth, J. L., & Siegler, R. S. (2008). Numerical Magnitude Presentations Infleunce Arithmetic Learning. *Child Development*, *79*(4), 1016–1031. https://doi.org/10.1111/j.1467-8624.2008.01173.x

Bricolo, E., Shallice, T., Priftis, K., & Meneghello, F. (2000). Selective space transformation deficit in a patient with spatial agnosia. *Neurocase*, *6*(4), 307–319. https://doi.org/10.1080/13554790008402779

Bruandet, M., Molko, N., Cohen, L., & Dehaene, S. (2004). A cognitive characterization of dyscalculia in Turner syndrome. *Neuropsychologia*, *42*(3), 288–298. https://doi.org/10.1016/j.neuropsychologia.2003.08.007

Buiatti, T., Mussoni, A., Toraldo, A., Skrap, M., & Shallice, T. (2011). Two qualitatively different impairments in making rotation operations. *Cortex*, *47*(2), 166–179. https://doi.org/10.1016/j.cortex.2009.10.006

Bull, R., Espy, K. A., & Wiebe, S. a. (2008). Short-term memory, working memory, and executive functioning in preschoolers: Longitudinal predictors of mathematical achievement at age 7 years. *Developmental Neuropsychology*, *33*(3), 205–228. https://doi.org/10.1080/87565640801982312

Butterworth, B. (1999). *The mathematical brain*. London: Macmillan.

Butterworth, B. (2005). Developmental Dyscalculia. In J. I. D. Campbell (Ed.), *Handbook of Mathematical Cognition* (pp. 455–467). Hove: PsychologyPress.

Butterworth, B. (2010). Foundational numerical capacities and the origins of dyscalculia. *Trends in Cognitive Sciences*, *14*(12), 534–541. https://doi.org/10.1016/j.tics.2010.09.007

Butterworth, B., & Walsh, V. (2011). Neural basis of mathematical cognition. *Current Biology*, *21*(16), R618-21. https://doi.org/10.1016/j.cub.2011.07.005

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002a). Rey-Osterrieth complex figure: normative values in an Italian population sample. *Neurological Sciences*, *22*(6), 443–447. https://doi.org/10.1007/s100720200003

Caffarra, P., Vezzadini, G., Dieci, F., Zonato, F., & Venneri, A. (2002b). Una versione abbreviata del test di Stroop: dati normativi nella popolazione italiana. *Nuova Rivista Di Neurologia*, *12*(4), 111–115. Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=14013019

Campanella, F., Shallice, T., Ius, T., Fabbro, F., & Skrap, M. (2014). Impact of brain tumour location on emotion and personality: A voxel-based lesion-symptom mapping study on mentalization processes. *Brain*, *137*(9), 2532–2545. https://doi.org/10.1093/brain/awu183

Campbell, J. I. D., & Graham, D. J. (1985). Mental multiplication skill: Structure, process, and acquisition. *Canadian Journal of Psychology*, *39*(2), 338–366. https://doi.org/10.1037/h0080065

Cannon, J., & Ginsburg, H. P. (2008). "Doing the Math": Maternal Beliefs About Early Mathematics Versus Language Learning. *Early Education & Development*, *19*(2), 238–260. https://doi.org/10.1080/10409280801963913

Cappelletti, M. (2015). *The Neuropsychology of Acquired Number and Calculation Disorders*. (R. Cohen Kadosh & A. Dowker, Eds.), *The Oxford Handbook fof Numerical Cognition* (Vol. 1). Oxford: Oxford University Press. https://doi.org/10.1093/oxfordhb/9780199642342.013.58

Cappelletti, M., Butterworth, B., & Kopelman, M. (2001). Spared numerical abilities in a case of semantic dementia. *Neuropsychologia*. https://doi.org/10.1016/S0028-3932(01)00035-5

Cappelletti, M., Butterworth, B., & Kopelman, M. (2012). Numeracy skills in patients with degenerative disorders and focal brain lesions: A neuropsychological investigation. *Neuropsychology*, *26*(1), 1–19. https://doi.org/10.1037/a0026328

Cappelletti, M., Didino, D., Stoianov, I., & Zorzi, M. (2014). Number skills are maintained in healthy ageing. *Cognitive Psychology*, *69*, 25–45. https://doi.org/10.1016/j.cogpsych.2013.11.004

Cappelletti, M., Gessaroli, E., Hithersay, R., Mitolo, M., Didino, D., Kanai, R., … Walsh, V. (2013). Transfer of Cognitive Training across Magnitude Dimensions Achieved with Concurrent Brain Stimulation of the Parietal Lobe. *The Journal of Neuroscience*, *33*(37), 14899–14907. https://doi.org/10.1523/JNEUROSCI.1692-13.2013

Carey, S. (2004). Bootstrapping and the origin of concepts. *Daedalus*, *133*(1), 59–68. https://doi.org/10.1162/001152604772746701

Carey, S. (2009). Where Our Number Concepts Come From. *The Journal of Philosophy*, *106*(4), 220–254. https://doi.org/10.5840/jphil2009106418

Carlesimo, G. A., Caltagirone, C., Gainotti, G., Fadda, L., Gallassi, R., Lorusso, S., … Parnetti, L. (1996). The Mental Deterioration Battery: Normative Data, Diagnostic Reliability and Qualitative Analyses of Cognitive Impairment. *European Neurology*, *36*(6), 378–384. https://doi.org/10.1159/000117297

Carlomagno, S., Iavarone, A., Nolte, G., Bourène, G., Martin, C., & Deloche, G. (1999). Dyscalculia in the early stages of Alzheimer's disease. *Acta Neurologica Scandinavica*, *99*(3), 166–74. https://doi.org/10.1111/j.1600-0404.1999.tb07339.x

Christakis, D. A. (2009, January). The effects of infant media usage: What do we know and what should we learn? *Acta Paediatrica*. https://doi.org/10.1111/j.1651-2227.2008.01027.x

Cipolotti, L. (1995). Multiple routes for reading words, why not numbers? evidence from a case of arabic numeral dyslexia. *Cognitive Neuropsychology*, *12*(3), 313–342. https://doi.org/10.1080/02643299508252001

Cipolotti, L., & Butterworth, B. (1995). Toward a multiroute model of number processing: Impaired number transcoding with preserved calculation skills. *Journal of Experimental Psychology: General*, *124*(4), 375–390. https://doi.org/10.1037/0096-3445.124.4.375

Cipolotti, L., Butterworth, B., & Denes, G. (1991). A specific deficit for numbers in a case of dense acalculia. *Brain*, *114*(6), 2619–2637. https://doi.org/10.1093/brain/114.6.2619

Cipolotti, L., Butterworth, B., & Warrington, E. K. (1994). From "One thousand nine hundred and forty-five" to 1000,945. *Neuropsychologia*, *32*(4), 503–509. https://doi.org/10.1016/0028-3932(94)90094-9

Cipolotti, L., & van Harskamp, N. (2001). Disturbances of number processing and calculation. In R. S. Berndt (Ed.), *Handbook of Neuropsychology* (Vol. 3, pp. 305–334). Amsterdam: Elsevier Science Ltd.

Cohen, L., Dehaene, S., & Verstichel, P. (1994). Number words and number non-words: A case of deep dyslexia extending to arabic numerals. *Brain*, *117*(2), 267–279. https://doi.org/10.1093/brain/117.2.267

Cohen Kadosh, R., Cohen Kadosh, K., Schuhmann, T., Kaas, A., Goebel, R., Henik, A., & Sack, A. T. (2007). Virtual Dyscalculia Induced by Parietal-Lobe TMS Impairs Automatic Magnitude Processing. *Current Biology*, *17*(8), 689–693. https://doi.org/10.1016/j.cub.2007.02.056

Cona, G., Scarpazza, C., Sartori, G., Moscovitch, M., & Bisiacchi, P. S. (2015, May 1). Neural bases of prospective memory: A meta-analysis and the "Attention to Delayed Intention" (AtoDI) model. *Neuroscience and Biobehavioral Reviews*. Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2015.02.007

Corradi-Dell'Acqua, C., Hofstetter, C., & Vuilleumier, P. (2011). Felt and Seen Pain Evoke the Same Local Patterns of Cortical Activity in Insular and Cingulate Cortex. *Journal of Neuroscience*, *31*(49), 17996–18006. https://doi.org/10.1523/JNEUROSCI.2686-11.2011

Cowell, S. F., Egan, G. F., Code, C., Harasty, J., & Watson, J. D. (2000). The functional neuroanatomy of simple calculation and number repetition: A parametric PET activation study. *NeuroImage*, *12*(5), 565–573. https://doi.org/10.1006/nimg.2000.0640

Crawford, J. R., & Garthwaite, P. H. (2006). Comparing Patients' Predicted Test Scores From a Regression Equation With Their Obtained Scores: A Significance Test and Point Estimate of Abnormality With Accompanying Confidence Limits. *Neuropsychology*, *20*(3), 259–271. https://doi.org/10.1037/0894-4105.20.3.259

Cutting, L. E., Koth, C. W., & Denckla, M. B. (2000). How children with neurofibromatosis type 1 differ from "typical" learning disabled clinic attenders: nonverbal learning disabilities revisited.

Developmental Neuropsychology, *17*(1), 29–47. https://doi.org/10.1207/S15326942DN1701_02
Dahmen, W., Hartje, W., Büssing, A., & Sturm, W. (1982). Disorders of calculation in aphasic patients-Spatial and verbal components. *Neuropsychologia*, *20*(2), 145–153. https://doi.org/10.1016/0028-3932(82)90004-5
Darzins, P., Molloy, W., & Strang, D. (2004). *Who Can Decide?: The Six Step Capacity Assessment Process*. Memory Australia Press. Retrieved from https://books.google.it/books?id=6tvYAAAACAAJ
De Hevia, M. D., Vallar, G., & Girelli, L. (2008, October). Visualizing numbers in the mind's eye: The role of visuo-spatial processes in numerical abilities. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2008.05.015
De Smedt, B., Verschaffel, L., & Ghesquière, P. (2009). The predictive value of numerical magnitude comparison for individual differences in mathematics achievement. *Journal of Experimental Child Psychology*, *103*(4), 469–479. https://doi.org/10.1016/j.jecp.2009.01.010
Dehaene, S., & Cohen, L. (1995). Towards an anatomical and functional model of number processing. *Mathematical Cognition*, *1*(1), 83–120.
Dehaene, S., & Cohen, L. (1997). Cerebral pathways for calculation: double dissociation between rote verbal and quantitative knowledge of arithmetic. *Cortex*, *33*(2), 219–250. https://doi.org/10.1016/S0010-9452(08)70002-9
Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three parietal circuits for number processing. *Cognitive Neuropsychology*, *20*(3), 487–506. https://doi.org/10.1080/02643290244000239
Delazer, M., & Bartha, L. (2001). Transcoding and calculation in aphasia. *Aphasiology*, *15*(7), 649–679. https://doi.org/10.1080/02687040143000104
Delazer, M., & Denes, G. (1998). Writing Arabic Numerals in an Agraphic Patient. *Brain and Language*, *64*(2), 257–266. https://doi.org/10.1006/brln.1998.1971
Delazer, M., Domahs, F., Bartha, L., Brenneis, C., Lochy, A., Trieb, T., & Benke, T. (2003). Learning complex arithmetic - An fMRI study. *Cognitive Brain Research*, *18*(1), 76–88. https://doi.org/10.1016/j.cogbrainres.2003.09.005
Delazer, M., Domahs, F., Lochy, A., Karner, E., Benke, T., & Poewe, W. (2004). Number processing and basal ganglia dysfunction: A single case study. *Neuropsychologia*, *42*(8), 1050–1062. https://doi.org/10.1016/j.neuropsychologia.2003.12.009
Delazer, M., Girelli, L., Granà, A., & Domahs, F. (2003). Number processing and calculation - Normative data from healthy adults. *The Clinical Neuropsychologist*, *17*(789543011), 331–350. https://doi.org/10.1076/clin.17.3.331.18092
Delazer, M., Girelli, L., Semenza, C., & Denes, G. (1999). Numerical skills and aphasia. *Journal of the International Neuropsychological Society*, *5*(3), 213–221. https://doi.org/10.1017/S1355617799533043
Delazer, M., Karner, E., Proell, S., & Benke, T. (2006). Counting complex dot patterns in Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, *28*(5), 721–31. https://doi.org/10.1080/13803390591000819
Delazer, M., Karner, E., Zamarian, L., Donnemiller, E., & Benke, T. (2006). Number processing in posterior cortical atrophy - A neuropsycholgical case study. *Neuropsychologia*, *44*(1), 36–51. https://doi.org/10.1016/j.neuropsychologia.2005.04.013
Delazer, M., Kemmler, G., & Benke, T. (2013). Health numeracy and cognitive decline in advanced age. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *20*(6), 639–59. https://doi.org/10.1080/13825585.2012.750261
Della Puppa, A., De Pellegrin, S., D'Avella, E., Gioffrè, G., Munari, M., Saladini, M., … Semenza, C. (2013). Right parietal cortex and calculation processing: intraoperative functional mapping of multiplication and addition in patients affected by a brain tumor. *Journal of Neurosurgery*, *119*(5), 1107–1111. https://doi.org/10.3171/2013.6.JNS122445
Della Puppa, A., De Pellegrin, S., Salillas, E., Grego, A., Lazzarini, A., Vallesi, A., … Semenza, C. (2015). Functional mapping of left parietal areas involved in simple addition and multiplication. A single-case study of qualitative analysis of errors. *Journal of Neuropsychology*, *9*(2), 330–335. https://doi.org/10.1111/jnp.12043
Deloche, G., & Seron, X. (1982a). From one to 1: An analysis of transcoding process by means of neuropsychological data. *Cognition*, *12*(2), 119–149. https://doi.org/10.1016/0010-0277(82)90009-9
Deloche, G., & Seron, X. (1982b). From three to 3: A differential analysis of skills in transcoding quantities between patients with broca's and wernicke's aphasia. *Brain*, *105*(4), 719–733. https://doi.org/10.1093/brain/105.4.719

Deloche, G., & Seron, X. (1987). Numerical transcoding: A general production model. In G. Deloche & X. Seron (Eds.), *Mathematical Disabilities: A Cognitive Neuropsychological Perspective* (pp. 137–170). Hillsdale, NJ: Lawrence Erlbaum Associates.

Demakis, G. J. (2012). *Civil Capacities in Clinical Neuropsychology: Research Findings and Practical Applications*. *Archives of Clinical Neuropsychology* (Vol. 27). New York: Oxford University Press.

Descheemaeker, M. J., Plasschaert, E., Frijns, J. P., & Legius, E. (2013). Neuropsychological profile in adults with neurofibromatosis type 1 compared to a control group. *Journal of Intellectual Disability Research*, *57*(9), 874–886. https://doi.org/10.1111/j.1365-2788.2012.01648.x

Desoete, A., Ceulemans, A., De Weerdt, F., & Pieters, S. (2012). Can we predict mathematical learning disabilities from symbolic and non-symbolic comparison tasks in kindergarten? Findings from a longitudinal study. *The British Journal of Educational Psychology*, *82*(Pt 1), 64–81. https://doi.org/10.1348/2044-8279.002002

Doricchi, F., Guariglia, P., Gasparini, M., & Tomaiuolo, F. (2005). Dissociation between physical and mental number line bisection in right hemisphere brain damage. *Nature Neuroscience*, *8*(12), 1663–1665. https://doi.org/10.1038/nn1563

Dreer, L. E., DeVivo, M. J., Novack, T. a., & Marson, D. C. (2012). Financial capacity following traumatic brain injury: A six-month longitudinal study. *Rehabilitation Psychology*, *57*(1), 5–12. https://doi.org/10.1037/a0025818

Duverne, S., & Lemaire, P. (2005). Aging and mental arithmetic. In J. I. D. Campbell (Ed.), *Handbook of Mathematical Cognition* (pp. 397–412). Hove: PsychologyPress.

Dye, M. W. G., & Bavelier, D. (2004). Playing video games enhances visual attention in children. *Journal of Vision*, *4*(11), 40–40. https://doi.org/10.1167/4.11.40

Espy, K. A., McDiarmid, M. M., Cwik, M. F., Stalets, M. M., Hamby, A., & Senn, T. E. (2004). The Contribution of Executive Functions to Emergent Mathematic Skills in Preschool Children. *Developmental Neuropsychology*, *26*(1), 465–486. https://doi.org/10.1207/s15326942dn2601_6

Feigenson, L., Dehaene, S., & Spelke, E. (2004). Core systems of number. *Trends in Cognitive Sciences*, *8*(7), 307–314. https://doi.org/10.1016/j.tics.2004.05.002

Ferner, R. E., Hughes, R. A. C., & Weinman, J. (1996). Intellectual impairment in neurofibromatosis 1. *Journal of the Neurological Sciences*, *138*(1–2), 125–133. https://doi.org/10.1016/0022-510X(96)00022-6

Fletcher, K. L., & Reese, E. (2005). Picture book reading with young children: A conceptual framework. *Developmental Review*, *25*(1), 64–103. https://doi.org/10.1016/j.dr.2004.08.009

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Furumoto, H. (2006). Pure misallocation of "0" in number transcoding: A new symptom of right cerebral dysfunction. In *Brain and Cognition* (Vol. 60, pp. 128–138). https://doi.org/10.1016/j.bandc.2005.10.002

Gardini, S., Cuetos, F., Fasano, F., Pellegrini, F. F., Marchi, M., Venneri, A., & Caffarra, P. (2013). Brain structural substrates of semantic memory decline in mild cognitive impairment. *Current Alzheimer Research*, *10*(4), 373–389. https://doi.org/10.2174/1567205011310040004

Gathercole, S. E., Pickering, S. J., Knight, C., & Stegmann, Z. (2004). Working memory skills and educational attainment: Evidence from national curriculum assessments at 7 and 14 years of age. *Applied Cognitive Psychology*, *18*(1), 1–16. https://doi.org/10.1002/acp.934

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., … Winblad, B. (2006). Mild cognitive impairment. *The Lancet*, *367*(9518), 1262–1270. https://doi.org/10.1016/S0140-6736(06)68542-5

Geary, D. C. (2011). Cognitive predictors of achievement growth in mathematics: a 5-year longitudinal study. *Developmental Psychology*, *47*(6), 1539–1552. https://doi.org/10.1037/a0025510

Geary, D. C., Bow-Thomas, C. C., & Yao, Y. (1992). Counting knowledge and skill in cognitive addition: A comparison of normal and mathematically disabled children. *Journal of Experimental Child Psychology*, *54*(3), 372–391. https://doi.org/10.1016/0022-0965(92)90026-3

Gelman, R., & Gallistel, C. R. (1986). *The child's understanding of number*. Cambridge, MA: Harvard University Press.

Gerstenecker, A., Eakin, A., Triebel, K., Martin, R., Swenson-Dravis, D., Petersen, R. C., & Marson, D. (2016). Age and education corrected older adult normative data for a short form version of the

Financial Capacity Instrument. *Psychological Assessment*, *28*(6), 737–749. https://doi.org/10.1037/pas0000159

Ginsburg, H. P., & Baroody, A. J. (1990). *Test of Early Mathematics Ability* (2nd ed.). Austin, TX: Pro-Ed.

Giovagnoli, A. R., Del Pesce, M., Mascheroni, S., Simoncelli, M., Laiacona, M., & Capitani, E. (1996). Trail making test: normative values from 287 normal adult controls. *The Italian Journal of Neurological Sciences*, *17*(4), 305–309. https://doi.org/10.1007/BF01997792

Girelli, L., Delazer, M., Semenza, C., & Denes, G. (1996). The Representation Of Arithmetical Facts: Evidence from two Rehabilitation Studies. *Cortex*, *32*(1), 49–66. https://doi.org/10.1016/S0010-9452(96)80016-5

Göbel, S., Walsh, V., & Rushworth, M. F. S. (2001). The mental number line and the human angular gyrus. *NeuroImage*, *14*(6), 1278–1289. https://doi.org/10.1006/nimg.2001.0927

Goetz, T., Bieg, M., Ludtke, O., Pekrun, R., & Hall, N. C. (2013). Do Girls Really Experience More Anxiety in Mathematics? *Psychological Science*, *24*(10), 2079–2087. https://doi.org/10.1177/0956797613486989

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews. Neuroscience*, *13*(7), 491–505. https://doi.org/10.1038/nrn3256

Grafman, J., Passafiume, D., Faglioni, P., & Boller, F. (1982). Calculation Disturbances in Adults with Focal Hemispheric Damage. *Cortex*, *18*(1), 37–49. https://doi.org/10.1016/S0010-9452(82)80017-8

Granà, A., Hofer, R., & Semenza, C. (2006). Acalculia from a right hemisphere lesion. Dealing with “where” in multiplication procedures. *Neuropsychologia*, *44*(14), 2972–2986. https://doi.org/10.1016/j.neuropsychologia.2006.06.027

Granà, A., Lochy, A., Girelli, L., Seron, X., & Semenza, C. (2003). Transcoding zeros within complex numerals. *Neuropsychologia*, *41*(12), 1611–1618. https://doi.org/10.1016/S0028-3932(03)00109-X

Griffith, H. R., Belue, K., Sicola, A., Krzywanski, S., Zamrini, E., Harrell, L., & Marson, D. C. (2003). Impaired financial abilities in mild cognitive impairment: a direct assessment approach. *Neurology*, *60*(3), 449–457. https://doi.org/10.1212/WNL.60.3.449

Griffith, H. R., Okonkwo, O. C., den Hollander, J. A., Belue, K., Lanza, S., Harrell, L. E., … Marson, D. C. (2007). Brain Proton MRS is Correlated with Financial Abilities in Patients with Alzheimer’s Disease. *Brain Imaging and Behavior*, *1*(1–2), 23–29. https://doi.org/10.1007/s11682-007-9002-3

Griffith, H. R., Stewart, C. C., Stoeckel, L. E., Okonkwo, O. C., Den Hollander, J. A., Martin, R. C., … Marson, D. C. (2010). Magnetic resonance imaging volume of the angular gyri predicts financial skill deficits in people with amnestic mild cognitive impairment. *Journal of the American Geriatrics Society*, *58*(2), 265–274. https://doi.org/10.1111/j.1532-5415.2009.02679.x

Grisso, T. (1986). *Evaluating competencies : forensic assessments and instruments*. *Perspectives in law & psychology* (Vol. 7). New York: Plenum Press.

Halberda, J., & Feigenson, L. (2008). Developmental change in the acuity of the “Number Sense”: The Approximate Number System in 3-, 4-, 5-, and 6-year-olds and adults. *Developmental Psychology*, *44*(5), 1457–1465. https://doi.org/10.1037/a0012682

Halberda, J., Mazzocco, M. M. M., & Feigenson, L. (2008). Individual differences in non-verbal number acuity correlate with maths achievement. *Nature*, *455*, 665–668. https://doi.org/10.1038/nature07246

Halpern, C., McMillan, C., Moore, P., Dennis, K., & Grossman, M. (2003). Calculation impairment in neurodegenerative diseases. *Journal of the Neurological Sciences*, *208*(1–2), 31–38. https://doi.org/10.1016/S0022-510X(02)00416-1

Hartje, W. (1987). The effect of spatial disorders on atithmetic skills. In G. Deloche & X. Seron (Eds.), *Mathematical Disabilities: A Cognitive Neuropsychological Perspective* (pp. 121–135). Hillsdale, NJ: Lawrence Erlbaum Associates.

Hécaen, H. (1962). Clinical symptomatology in right and left hemispheric lesions. In V. B. Montcastle (Ed.), *Interhemispheric relations and cerebral dominance* (pp. 215–243). Baltimore: John Hopkins. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/13905821

Hécaen, H., & Angelergues, R. (1961). Etude anatomo-clinique de 280 cas de lésions rétro-rolandiques unilatérales des hémisphères cérébraux. *L’encéphale*, *6*, 533–562.

Heilman, K. M., Watson, R. T., Valenstein, E., & Damasio, A. R. (1983). Localization of lesions in neglect. In A. Kertesz (Ed.), *Localization in Neuropsychology* (pp. 471–492). Cambridge, MA: Academic Press.

Henschen, S. E. (1926). On the function of the right hemisphere of the brain in relation to the left in speech, music and calculation. *Brain*, *49*(1), 110–123. https://doi.org/10.1093/brain/49.1.110

Hitch, G. J. (1996). Temporal Grouping Effects in Immediate Recall: A Working Memory Analysis. *The*

Quarterly Journal of Experimental Psychology: Section A, *49*(1), 116–139. https://doi.org/10.1080/713755609
Hittmair-Delazer, M., Semenza, C., & Denes, G. (1994). Concepts and facts in calculation. *Brain*, *117*(4), 715–728. https://doi.org/10.1093/brain/117.4.715
Hogan, D., Etz, K., & Tudge, J. (1999). Reconsidering the role of children in family research: Conceptual and methodological issues. In C. Shehan (Ed.), *Contemporary perspectives on family research* (Vol. 1, pp. 93–105). Stamford, CT: JAI Press.
Holmes, G. (1918). Disturbances of Visual Orientation. *The British Journal of Ophthalmology*, *2*(9), 449–468. https://doi.org/10.1136/bjo.2.9.449
Houghton, G. (1990). The problem of serial order: A neural network model of sequence learning and recall. In R. Dale, C. S. Mellish, & M. Zock (Eds.), *Current Research in Natural Language Generation* (pp. 287–319). San Diego, CA: Academic Press Professional, Inc.
Huntsinger, C. S., Jose, P. E., Larson, S. L., Balsink Krieg, D., & Shaligram, C. (2000). Mathematics, vocabulary, and reading development in Chinese American and European American children over the primary school years. *Journal of Educational Psychology*, *92*(4), 745–760. https://doi.org/10.1037/0022-0663.92.4.745
Hurtado, N., Marchman, V. A., & Fernald, A. (2008). Does input influence uptake? Links between maternal talk, processing speed and vocabulary size in Spanish-learning children. *Developmental Science*, *11*(6), F31–F39. https://doi.org/10.1111/j.1467-7687.2008.00768.x
Hyman, S. L., Shores, E. A., & North, K. N. (2005). The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. *Neurology*, *65*(7), 1037–1044. https://doi.org/10.1212/01.wnl.0000179303.72345.ce
Izard, V., Sann, C., Spelke, E. S., & Streri, A. (2009). Newborn infants perceive abstract numbers. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(25), 10382–10385. https://doi.org/10.1073/pnas.0812142106
Jackson, M., & Warrington, E. K. (1986). Arithmetic Skills in Patients with Unilateral Cerebral Lesions. *Cortex*, *22*(4), 611–620. https://doi.org/10.1016/S0010-9452(86)80020-X
Jordan, N. C., Kaplan, D., Nabors Oláh, L., & Locuniak, M. N. (2006). Number sense growth in kindergarten: A longitudinal investigation of children at risk for mathematics difficulties. *Child Development*, *77*(1), 153–175. https://doi.org/10.1111/j.1467-8624.2006.00862.x
Jordan, N. C., Levine, S. C., & Huttenlocher, J. (1994). Development of calculation abilities in middle- and low-income children after formal instruction in school. *Journal of Applied Developmental Psychology*, *15*(2), 223–240. https://doi.org/10.1016/0193-3973(94)90014-0
Joubert, S., Brambati, S. M., Ansado, J., Barbeau, E. J., Felician, O., Didic, M., … Kergoat, M.-J. (2010). The cognitive and neural expression of semantic memory impairment in mild cognitive impairment and early Alzheimer's disease. *Neuropsychologia*, *48*(4), 978–988. https://doi.org/10.1016/j.neuropsychologia.2009.11.019
Karnath, H. O., & Baier, B. (2010). Right insula for our sense of limb ownership and self-awareness of actions. *Brain Structure and Function*, *214*, 1–7. https://doi.org/10.1007/s00429-010-0250-4
Karnath, H. O., Berger, M. F., Küker, W., & Rorden, C. (2004). The Anatomy of Spatial Neglect based on Voxelwise Statistical Analysis: A Study of 140 Patients. *Cerebral Cortex*, *14*(10), 1164–1172. https://doi.org/10.1093/cercor/bhh076
Karnath, H. O., Rorden, C., & Ticini, L. F. (2009). Damage to white matter fiber tracts in acute spatial neglect. *Cerebral Cortex*, *19*(10), 2331–2337. https://doi.org/10.1093/cercor/bhn250
Katz, S. (1983). Assessing Self-maintenance: Activities of Daily Living, Mobility, and Instrumental Activities of Daily Living. *Journal of the American Geriatrics Society*, *31*(12), 721–727. https://doi.org/10.1111/j.1532-5415.1983.tb03391.x
Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. a, & Jaffe, M. W. (1963). Studies of illness in the aged. The Index of ADL: A Standardized Measure of Biological and Psychosocial Function. *Journal of the American Medical Association*, *185*, 914–919. https://doi.org/10.1001/jama.1963.03060120024016
Kershaw, M. M., & Webber, L. S. (2004). Dimensions of Financial Competence. *Psychiatry, Psychology and Law*, *11*(2), 338–349. https://doi.org/10.1375/1321871042707241
Kershaw, M. M., & Webber, L. S. (2008). Assessment of financial competence. *Psychiatry, Psychology and Law*, *15*(1), 40. https://doi.org/10.1080/13218710701873965
Kleemans, T., Peeters, M., Segers, E., & Verhoeven, L. (2012). Child and home predictors of early numeracy skills in kindergarten. *Early Childhood Research Quarterly*, *27*(3), 471–477.

https://doi.org/10.1016/j.ecresq.2011.12.004

Kroesbergen, E. H., Van Luit, J. E. H., Van Lieshout, E. C. D. M., Van Loosbroek, E., & Van de Rijt, B. a. M. (2009). Individual Differences in Early Numeracy: The Role of Executive Functions and Subitizing. *Journal of Psychoeducational Assessment*, *27*(3), 226–236. https://doi.org/10.1177/0734282908330586

Kurth, F., Zilles, K., Fox, P. T., Laird, A. R., & Eickhoff, S. B. (2010, June). A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. *Brain Structure and Function*, pp. 1–16. https://doi.org/10.1007/s00429-010-0255-z

Lai, J. M., Gill, T. M., Cooney, L. M., Bradley, E. H., Hawkins, K. A., & Karlawish, J. H. (2008). Everyday Decision-Making Ability in Older Persons With Cognitive Impairment. *The American Journal of Geriatric Psychiatry*, *16*(8), 693–696. https://doi.org/10.1097/JGP.0b013e31816c7b54

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., … Fox, P. T. (2000). Automated Talairach Atlas labels for functional brain mapping. *Human Brain Mapping*, *10*(3), 120–131. https://doi.org/10.1002/1097-0193(200007)10:3<120::AID-HBM30>3.0.CO;2-8

Lawton, M. P., & Brody, E. M. (1969). Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living. *Gerontologist*, *9*(3), 179–186. https://doi.org/10.1093/geront/9.3_Part_1.179

LeFevre, J.-A., Clarke, T., & Stringer, A. P. (2002). Influences of Language and Parental Involvement on the Development of Counting Skills: Comparisons of French- and English-speaking Canadian Children. *Early Child Development and Care*, *172*(3), 283–300. https://doi.org/10.1080/03004430212127

LeFevre, J.-A., Kwarchuk, S. L., Smith-Chant, B. L., Fast, L., Kamawar, D., & Bisanz, J. (2009). Home numeracy experiences and children's math performance in the early school years. *Canadian Journal of Behavioural Science*, *41*(2), 55–66. https://doi.org/10.1037/a0014532

LeFevre, J.-A., Polyzoi, E., Skwarchuk, S.-L., Fast, L., & Sowinski, C. (2010). Do home numeracy and literacy practices of Greek and Canadian parents predict the numeracy skills of kindergarten children? *International Journal of Early Years Education*, *18*(1), 55–70. https://doi.org/10.1080/09669761003693926

Lemaire, P., & Arnaud, L. (2008). Young and older adults' strategies in complex arithmetic. *American Journal of Psychology*, *121*(1), 1–16. https://doi.org/10.2307/20445440

Leslie, A. M., Gelman, R., & Gallistel, C. R. (2008). The generative basis of natural number concepts. *Trends in Cognitive Sciences*, *12*(6), 213–218. https://doi.org/10.1016/j.tics.2008.03.004

Levine, T. M., Materek, A., Abel, J., O'Donnell, M., & Cutting, L. E. (2006). Cognitive Profile of Neurofibromatosis Type 1. *Seminars in Pediatric Neurology*, *13*(1), 8–20. https://doi.org/10.1016/j.spen.2006.01.006

Lichtenberg, P. A., Qualls, S. H., & Smyer, M. A. (2015). Competency and decision-making capacity: Negotiating health and financial decision making. In P. A. Lichtenberg, B. T. Mast, B. D. Carpenter, & J. Wetherell (Eds.), *APA handbook of clinical geropsychology, Vol. 2: Assessment, treatment, and issues of later life.* (pp. 553–578). Washington: American Psychological Association. https://doi.org/http://dx.doi.org/10.1037/14459-021

Lochy, A., Domahs, F., Bartha, L., & Delazer, M. (2004). Specific order impairment in arabic number writing: A case-study. *Cognitive Neuropsychology*, *21*(5), 555–575. https://doi.org/10.1080/02643290342000618

Lövde, M., Bäckman, L., Lindenberger, U., Schaefer, S., & Schmiedek, F. (2010). A Theoretical Framework for the Study of Adult Cognitive Plasticity. *Psychological Bulletin*, *136*(4), 659–676. https://doi.org/10.1037/a0020080

Lucangeli, D., Tressoldi, P., & Re, A. M. (2012). Path to Numbers Writing: A Longitudinal Study with Children from 3.5 to 5.5 Years Old. *Journal of Educational and Developmental Psychology*, *2*(2), 20–31. https://doi.org/10.5539/jedp.v2n2p20

Magni, E., Binetti, G., Padovani, A., Cappa, S. F., Bianchetti, A., & Trabucchi, M. (1996). The Mini-Mental State Examination in Alzheimer's disease and multi-infarct dementia. *International Psychogeriatrics*, *8*, 127–134. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8805093

Maloney, E. A., Sattizahn, J. R., & Beilock, S. L. (2014). Anxiety and cognition. *Wiley Interdisciplinary Reviews: Cognitive Science*, *5*(4), 403–411. https://doi.org/10.1002/wcs.1299

Marson, D. C. (2013). Clinical and ethical aspects of financial capacity in dementia: A commentary. *American Journal of Geriatric Psychiatry*, *21*(4), 382–390. https://doi.org/10.1016/j.jagp.2013.01.033

Marson, D. C. (2015). Investigating Functional Impairment in Preclinical Alzheimer's Disease. *The Journal of Prevention of Alzheimer's Disease*, *2*(1), 4–6. https://doi.org/10.14283/jpad.2015.44

Marson, D. C., Hebert, K., & Solomon, A. C. (2012). Assessing civil competencies in older adults with dementia: Consent capacity, financial capacity, and testamentary capacity. In G. J. Larrabee (Ed.), *Forensic neuropsychology: A scientific approach (2nd ed.).* (pp. 401–437). Oxford University Press. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2011-27640-015&site=ehost-live

Marson, D. C., Martin, R. C., Wadley, V., Griffith, H. R., Snyder, S., Goode, P. S., … Harrell, L. E. (2009). Clinical interview assessment of financial capacity in older adults with mild cognitive impairment and Alzheimer's disease. *Journal of the American Geriatrics Society*, *57*(5), 806–814. https://doi.org/10.1111/j.1532-5415.2009.02202.x

Marson, D. C., Sawrie, S. M., Snyder, S., McInturff, B., Stalvey, T., Boothe, A., … Harrell, L. E. (2000). Assessing Financial Capacity in Patients With Alzheimer Disease: A conceptual model and prototype instrument. *Archives of Neurology*, *57*(6), 877–884. https://doi.org/10.1001/archneur.57.6.877

Marson, D. C., & Zebley, L. (2001). The Other Side of the Retirement Years: Cognitive Decline, Dementia, and Loss of Financial Capacity. *Journal of Retirement Planning*, *4*, 30–39. Retrieved from http://heinonline.org/HOL/Page?handle=hein.journals/jrlrp4&id=30&div=&collection=

Martin, R. C., Triebel, K., Dreer, L. E., Novack, T. A., Turner, C., & Marson, D. C. (2012). Neurocognitive Predictors of Financial Capacity in Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation*, *27*(6), E81–E90. https://doi.org/10.1097/HTR.0b013e318273de49

Martini, L., Domahs, F., Benke, T., & Delazer, M. (2003). Everyday numerical abilities in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *9*(6), 871–878. https://doi.org/10.1017/S1355617703960073

Maurer, S., Tanigawa, N., Sollmann, N., Hauck, T., Ille, S., Boeckh-Behrens, T., … Krieg, S. M. (2015). Non-invasive mapping of calculation function by repetitive navigated transcranial magnetic stimulation. *Brain Structure and Function*, *221*(8), 3927–3947. https://doi.org/10.1007/s00429-015-1136-2

Mazzocco, M. M. M. (2001). Math Learning Disability and Math LD Subtypes: Evidence from Studies of Turner Syndrome, Fragile X Syndrome, and Neurofibromatosis Type 1. *Journal of Learning Disabilities*, *34*(6), 520–533. https://doi.org/10.1177/002221940103400605

Mazzocco, M. M. M., Feigenson, L., & Halberda, J. (2011). Preschoolers' precision of the approximate number system predicts later school mathematics performance. *PLoS ONE*, *6*(9), e23749. https://doi.org/10.1371/journal.pone.0023749

McCloskey, M., Caramazza, A., Hopkins, J., And, U., Basili, A., Goodman, R., … Raskin, S. (1985). Cognitive Mechanisms in Number Processing and Calculation: Evidence from Dyscalculia. *Brain and Cognition*, *4*(2), 171–196.

McCloskey, M., Harley, W., & Sokol, S. M. (1991). Models of arithmetic fact retrieval: An evaluation in light of findings from normal and brain-damaged subjects. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *17*(3), 377–397. https://doi.org/10.1037/0278-7393.17.3.377

McKhann, G. M., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*(7), 939–944. https://doi.org/10.1212/WNL.34.7.939

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., … Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*, *7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

Melhuish, E. C., Sylva, K., Sammons, P., Siraj-Blatchford, I., Taggart, B., Phan, M. B., & Malin, A. (2008). The Early Years: Preschool Influence on Mathematics Achievement. *Science*, *321*(5893), 1161–1162. https://doi.org/10.1126/science.1158808

Menon, V., & Uddin, L. Q. (2010, June). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, pp. 1–13. https://doi.org/10.1007/s00429-010-0262-0

Merritt, D. J., & Brannon, E. M. (2013). Nothing to it: Precursors to a zero concept in preschoolers. *Behavioural Processes*, *93*, 91–97. https://doi.org/10.1016/j.beproc.2012.11.001

Miceli, G., & Capasso, R. (1999). Calculation and number processing in normality and pathology. In G. Denes & L. Pizzamiglio (Eds.), *Handbook of Neuropsychology* (pp. 583–612). Hove: Psychology Press.

Ming Chiu, M., & Xihua, Z. (2008). Family and motivation effects on mathematics achievement: Analyses of students in 41 countries. *Learning and Instruction*, *18*(4), 321–336.

https://doi.org/10.1016/j.learninstruc.2007.06.003
Monaco, M., Costa, A., Caltagirone, C., & Carlesimo, G. A. (2013). Forward and backward span for verbal and visuo-spatial data: standardization and normative data from an Italian adult population. *Neurological Sciences*, *34*(5), 749–754. https://doi.org/10.1007/s10072-012-1130-x
Moore, B. D. (2009). Potential influences on mathematical difficulties in children and adolescents with Neurofibromatosis, type 1. *Developmental Disabilities Research Reviews*, *15*(1), 45–51. https://doi.org/10.1002/ddrr.53
Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., & Berg, L. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of Neurology*, *58*(3), 397–405. https://doi.org/10.1001/archneur.58.3.397
Moye, J., & Marson, D. C. (2007). Assessment of Decision-Making Capacity in Older Adults: An Emerging Area of Practice and Research. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *62*(1), P3–P11. https://doi.org/10.1093/geronb/62.1.P3
Mussolin, C., Nys, J., Leybaert, J., & Content, A. (2012). Relationships between approximate number system acuity and early symbolic number abilities. *Trends in Neuroscience and Education*, *1*(1), 21–31. https://doi.org/10.1016/j.tine.2012.09.003
Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., … Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x
National Academies of Sciences Engineering and Medicine. (2016). *Informing Social Security's Process for Financial Capability Determination*. (P. S. Appelbaum, C. M. Spicer, & F. R. Valliere, Eds.). Washington, D.C.: National Academies Press. https://doi.org/10.17226/21922
Noël, M.-P., & Seron, X. (1995, November). Lexicalization errors in writing Arabic numerals: A single-case study. *Brain and Cognition*. https://doi.org/10.1006/brcg.1995.1274
North, K., Hyman, S., & Barton, B. (2002). Cognitive deficits in neurofibromatosis 1. *Journal of Child Neurology*, *17*(8), 605–612. https://doi.org/10.1177/088307380201700811
Novelli, G., Papagno, C., Capitani, E., Laiacona, M., Cappa, S. F., & Vallar, G. (1986). Tre test clinici di memoria verbale a lungo termine. Taratura su soggetti normali. *Archivio Di Psicologia Neurologia E Psichiatria*, *47*, 477–506. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7754088
Nucci, M., Mapelli, D., & Mondini, S. (2012). Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve. *Aging Clinical and Experimental Research*, *24*(3), 218–26. https://doi.org/10.3275/7800
Nygard, L. (2003). Instrumental activities of daily living: a stepping-stone towards Alzheimer's disease diagnosis in subjects with mild cognitive impairment? *Acta Neurologica Scandinavica*, *107*(s179), 42–46. https://doi.org/10.1034/j.1600-0404.107.s179.8.x
Obersteiner, A., Reiss, K., & Ufer, S. (2013). How training on exact or approximate mental representations of number can enhance first-grade students' basic number processing and arithmetic skills. *Learning and Instruction*, *23*(1), 125–135. https://doi.org/10.1016/j.learninstruc.2012.08.004
Okonkwo, O. C., Griffith, H. R., Vance, D. E., Marson, D. C., Ball, K. K., & Wadley, V. G. (2009). Awareness of Functional Difficulties in Mild Cognitive Impairment: A Multidomain Assessment Approach. *Journal of the American Geriatrics Society*, *57*(6), 978–984. https://doi.org/10.1111/j.1532-5415.2009.02261.x
Okonkwo, O. C., Wadley, V. G., Griffith, H. R., Ball, K., & Marson, D. C. (2006). Cognitive correlates of financial abilities in mild cognitive impairment. *Journal of the American Geriatrics Society*, *54*(11), 1745–1750. https://doi.org/10.1111/j.1532-5415.2006.00916.x
Okonkwo, O. C., Wadley, V. G., Griffith, H. R., Belue, K., Lanza, S., Zamrini, E. Y., … Marson, D. C. (2008). Awareness of Deficits in Financial Abilities in Patients With Mild Cognitive Impairment: Going Beyond Self-Informant Discrepancy. *American Journal of Geriatric Psychiatry*, *16*(8), 650–659. https://doi.org/10.1097/JGP.0b013e31817e8a9d
Orraca-Castillo, M., Estévez-Pérez, N., & Reigosa-Crespo, V. (2014). Neurocognitive profiles of learning disabled children with neurofibromatosis type 1. *Frontiers in Human Neuroscience*, *8*(June), 386. https://doi.org/10.3389/fnhum.2014.00386
Orsini, A., Grossi, D., Capitani, E., & Laiacona, M. (1987). Verbal and spatial immediate memory span:

normative data from 1335 item sand 112 children. *Italian Journal of Neurological Science*, *8*(6), 537–548.

Palmieri, A., Soraru, G., D'Ascenzo, C., Balestreri, S., Arcara, G., Ermani, M., … Semenza, C. (2013). Specific numerical processing impairment in ALS patients. *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, *14*(1), 6–12. https://doi.org/10.3109/17482968.2012.719235

Pan, Y., Gauvain, M., Liu, Z., & Cheng, L. (2006). American and Chinese parental involvement in young children's mathematics learning. *Cognitive Development*, *21*(1), 17–35. https://doi.org/10.1016/j.cogdev.2005.08.001

Park, J., & Brannon, E. M. (2013). Training the approximate number system improves math proficiency. *Psychological Science*, *24*(10), 2013–2019. https://doi.org/10.1177/0956797613482944

Parsons, J. E., Adler, T. F., & Kaczula, C. M. (1982). Socialization of Achievement Attitudes and Beliefs: Parental influences. *Child Development*, *53*(2), 310–321. https://doi.org/10.2307/1128973

Parsons, S., & Bynner, J. (2005). *Does Numeracy Matter More?* London: National Research and Development Centre for Adult Literacy and Numeracy, Institute of Education.

Passolunghi, M. C., & Lanfranchi, S. (2012). Domain-specific and domain-general precursors of mathematical achievement: A longitudinal study from kindergarten to first grade. *British Journal of Educational Psychology*, *82*(1), 42–63. https://doi.org/10.1111/j.2044-8279.2011.02039.x

Passolunghi, M. C., Mammarella, I. C., & Altoe, G. (2008). Cognitive abilities as precursors of the early acquisition of mathematical skills during first through second grades. *Developmental Neuropsychology*, *33*(3), 229–250. https://doi.org/10.1080/87565640801982320

Passolunghi, M. C., Vercelloni, B., & Schadee, H. (2007). The precursors of mathematics learning: Working memory, phonological ability and numerical competence. *Cognitive Development*, *22*(2), 165–184. https://doi.org/10.1016/j.cogdev.2006.09.001

Pavol, M., Hiscock, M., Massman, P., Moore Iii, B., Foorman, B., & Meyers, C. (2006). Neuropsychological function in adults with von Recklinghausen's neurofibromatosis. *Developmental Neuropsychology*, *29*(3), 509–26. https://doi.org/10.1207/s15326942dn2903_8

Payne, J. M., Hyman, S. L., Shores, E. A., & North, K. N. (2011). Assessment of executive function and attention in children with neurofibromatosis type 1: relationships between cognitive measures and real-world behavior. *Child Neuropsychology : A Journal on Normal and Abnormal Development in Childhood and Adolescence*, *17*(4), 313–329. https://doi.org/10.1080/09297049.2010.542746

Pertl, M.-T., Benke, T., Zamarian, L., Martini, C., Bodner, T., Karner, E., & Delazer, M. (2014). Do patients with mild cognitive impairment understand numerical health information? *Journal of Alzheimer's Disease*, *40*(3), 531–540. https://doi.org/10.3233/JAD-131895

Pesenti, M., Depoorter, N., & Seron, X. (2000). *Noncommutability of The N + 0 Arithmetical Rule: A Case Study of Dissociated Impairment*. *Cortex* (Vol. 36). https://doi.org/10.1016/S0010-9452(08)70853-0

Pesenti, M., Thioux, M., Seron, X., & De Volder, A. (2000). Neuroanatomical substrates of arabic number processing, numerical comparison, and simple addition: a PET study. *Journal of Cognitive Neuroscience*, *12*(3), 461–79. https://doi.org/10.1162/089892900562273

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., … Winblad, B. (2001). Current Concepts in Mild Cognitive Impairment. *Archives of Neurology*, *58*(12), 1985–1992. https://doi.org/10.1001/archneur.58.12.1985

Piazza, M., Pica, P., Izard, V., Spelke, E. S., & Dehaene, S. (2013). Education enhances the acuity of the nonverbal approximate number system. *Psychological Science*, *24*(6), 1037–1043. https://doi.org/10.1177/0956797612464057

Power, R. J. D., & Dal Martello, M. F. (1990). The dictation of Italian numerals. *Language and Cognitive Processes*, *5*(3), 237–254. https://doi.org/10.1080/01690969008402106

Power, R. J. D., & Dal Martello, M. F. (1997). From 834 to Eighty Thirty Four: The Reading of Arabic Numerals by Seven-year-old Children. *Mathematical Cognition*, *3*(1), 63–85. https://doi.org/10.1080/135467997387489

Price, G. R., Mazzocco, M. M. M., & Ansari, D. (2013). Why Mental Arithmetic Counts: Brain Activation during Single Digit Arithmetic Predicts High School Math Scores. *Journal of Neuroscience*, *33*(1), 156–163. https://doi.org/10.1523/JNEUROSCI.2936-12.2013

Priftis, K., Albanese, S., Meneghello, F., & Pitteri, M. (2013). Pure left neglect for Arabic numerals. *Brain and Cognition*, *81*(1), 118–123. https://doi.org/10.1016/j.bandc.2012.09.008

R Development Core Team, R. (2012). *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing. https://doi.org/10.1007/978-3-540-74686-7

Ramani, G. B., & Siegler, R. S. (2008). Promoting broad and stable improvements in low-income children's numerical knowledge through playing number board games. *Child Development*, *79*(2), 375–394. https://doi.org/10.1111/j.1467-8624.2007.01131.x

Reeve, R., Reynolds, F., Humberstone, J., & Butterworth, B. (2012). Stability and change in markers of core numerical competencies. *Journal of Experimental Psychology: General*, *141*(4), 649–666. https://doi.org/10.1037/a0027520

Riccardi, V. M., & Eichner, J. E. (1986). *Neurofibromatosis: phenotype, natural history, and pathogenesis*. Johns Hopkins University Press. Retrieved from https://books.google.it/books?id=RIJrAAAAMAAJ

Rodríguez-Ferreiro, J., Cuetos, F., Monsalve, A., Martínez, C., Pérez, A. J., & Venneri, A. (2012). Establishing the relationship between cortical atrophy and semantic deficits in Alzheimer's disease and mild cognitive impairment patients through voxel-based morphometry. *Journal of Neurolinguistics*, *25*(3), 139–149. https://doi.org/10.1016/j.jneuroling.2011.10.001

Rorden, C., & Brett, M. (2000). Stereotaxic Display of Brain Lesions. *Behavioural Neurology*, *12*(4), 191–200. https://doi.org/10.1155/2000/421719

Rorden, C., Karnath, H. O., & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of Cognitive Neuroscience*, *19*(7), 1081–1088. https://doi.org/10.1162/jocn.2007.19.7.1081

Rosenberg-Lee, M., Chang, T. T., Young, C. B., Wu, S., & Menon, V. (2011). Functional dissociations between four basic arithmetic operations in the human posterior parietal cortex: A cytoarchitectonic mapping study. *Neuropsychologia*, *49*(9), 2592–2608. https://doi.org/10.1016/j.neuropsychologia.2011.04.035

Rosselli, M., & Ardila, A. (1989). Calculation deficits in patients with right and left hemisphere damage. *Neuropsychologia*, *27*(5), 607–617. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L19150585%5Cnhttp://dx.doi.org/10.1016/0028-3932(89)90107-3%5Cnhttp://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=00283932&id=doi:10.1016%2F0028-3932%2889%2990107-3&atitle=Calculation+

Salillas, E., & Semenza, C. (2014). Mapping the Brain for Math. Reversible inactivation by direct cortical electrostimulation and transcranial magnetic stimulation. In R. Cohen Kadosh & A. Dowker (Eds.), *The Oxford Handbook of Numerical Cognition* (pp. 1–24). Oxford: Oxford University Press. https://doi.org/10.1093/oxfordhb/9780199642342.013.046

Salillas, E., Semenza, C., Basso, D., Vecchi, T., & Siegal, M. (2012). Single pulse TMS induced disruption to right and left parietal cortex on addition and multiplication. *NeuroImage*, *59*(4), 3159–3165. https://doi.org/10.1016/j.neuroimage.2011.10.093

Segulin, N., & Deponte, A. (2007). The evaluation of depression in the elderly: A modification of the geriatric depression scale (GDS). *Archives of Gerontology and Geriatrics*, *44*(2), 105–112. https://doi.org/10.1016/j.archger.2006.04.002

Sella, F., Berteletti, I., Lucangeli, D., & Zorzi, M. (2015). Varieties of Quantity Estimation in Children. *Developmental Psychology*, *51*(6), 758–770. https://doi.org/http://dx.doi.org/10.1037/a0039183

Semenza, C. (2008). Number Processing. In B. Stemmer & H. Whitaker (Eds.), *Handbook of the Neuroscience of Language* (pp. 219–227). Amsterdam: Elsevier. https://doi.org/10.1016/B978-0-08-045352-1.00021-5

Semenza, C., Bonollo, S., Polli, R., Busana, C., Pignatti, R., Iuculano, T., … Murgia, A. (2012). Genetics and mathematics: FMR1 premutation female carriers. *Neuropsychologia*, *50*(14), 3757–3763. https://doi.org/10.1016/j.neuropsychologia.2012.10.021

Semenza, C., Grana, A., & Girelli, L. (2006). On knowing about nothing: The processing of zero in single- and multi-digit multiplication. *Aphasiology*, *20*(9), 1105–1111. https://doi.org/10.1080/02687030600741659

Semenza, C., Meneghello, F., Arcara, G., Burgio, F., Gnoato, F., Facchini, S., … Butterworth, B. (2014). A new clinical tool for assessing numerical abilities in neurological diseases: numerical activities of daily living. *Frontiers in Aging Neuroscience*, *6*, 1–8. https://doi.org/10.3389/fnagi.2014.00112

Semenza, C., Pignatti, R., Bertella, L., Ceriani, F., Mori, I., Molinari, E., … Grugni, G. (2008). Genetics and mathematics: Evidence from Prader-Willi syndrome. *Neuropsychologia*, *46*(1), 206–212. https://doi.org/10.1016/j.neuropsychologia.2007.07.017

Semenza, C., Salillas, E., De Pellegrin, S., & Della Puppa, A. (2016). Balancing the 2 Hemispheres in Simple Calculation: Evidence From Direct Cortical Electrostimulation. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhw277

Seron, X., & Deloche, G. (1983). From 4 to four: A supplement to “from three to 3.” *Brain*, *106*(3), 735–744. https://doi.org/10.1093/brain/106.3.735
Seron, X., Deloche, G., & Noël, M.-P. (1991). Un transcodage des nombres chez l’enfant: La production des chiffres sous dictée. In J. Bideaud, C. Meljac, & J. P. Fischer (Eds.), *Les chemins du nombre* (pp. 303–328). Lille: Presses Universitaires de Lille.
Seron, X., & Fayol, M. (1994). Number transcoding in children: A functional analysis. *British Journal of Developmental Psychology*, *12*(3), 281–300. https://doi.org/10.1111/j.2044-835X.1994.tb00635.x
Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS) Recent Evidence and Development of a Shorter Version. *Clinical Gerontologist*, *5*(1–2), 165–173. https://doi.org/10.1300/J018v05n01_09
Sheldon, S. B., & Epstein, J. L. (2005). Involvement Counts: Family and Community Partnerships and Mathematics Achievement. *The Journal of Educational Research*, *98*(4), 196–207. https://doi.org/10.3200/JOER.98.4.196-207
Sherod, M. G., Griffith, H. R., Copeland, J., Belue, K., Krzywanski, S., Zamrini, E. Y., … Marson, D. C. (2009). Neurocognitive predictors of financial capacity across the dementia spectrum: Normal aging, mild cognitive impairment, and Alzheimer’s disease. *Journal of the International Neuropsychological Society*, *15*(2), 258–267. https://doi.org/10.1017/S1355617709090365
Shinoura, N., Suzuki, Y., Yamada, R., Tabei, Y., Saito, K., & Yagi, K. (2009). Damage to the right superior longitudinal fasciculus in the inferior parietal lobe plays a role in spatial neglect. *Neuropsychologia*, *47*(12), 2600–2603. https://doi.org/10.1016/j.neuropsychologia.2009.05.010
Siegler, R. S. (1988). Strategy choice procedures and the development of multiplication skill. *Journal of Experimental Psychology: General*, *117*(3), 258–275. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2971762
Siegler, R. S., & Booth, J. L. (2004). Development of numerical estimation in young children. *Child Development*, *75*(2), 428–444. https://doi.org/10.1111/j.1467-8624.2004.00684.x
Siegler, R. S., & Ramani, G. B. (2008). Playing linear numerical board games promotes low-income children’s numerical development. *Developmental Science*, *11*(5), 655–661. https://doi.org/10.1111/j.1467-7687.2008.00714.x
Singer, T., Critchley, H. D., & Preuschoff, K. (2009). A common role of insula in feelings, empathy and uncertainty. *Trends in Cognitive Sciences*, *13*(8), 334–340. https://doi.org/10.1016/j.tics.2009.05.001
Slick, D. J. (2006). Developments in neuropsychological assessment. In E. Strauss, E. M. Sherman, & O. Spreen (Eds.), *A compendium of neuropsychological tests: administration, norms, and commentary*. New York: Oxford University Press.
Sokol, S. M., McCloskey, M., Cohen, N. J., & Aliminosa, D. (1991). Cognitive representations and processes in arithmetic: inferences from the performance of brain-damaged subjects. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *17*(3), 355–376. https://doi.org/10.1037/0278-7393.17.3.355
Spelke, E. (2008). Effects of music instruction on developing cognitive systems at the foundations of mathematics and science. In C. H. Asbury & B. Rich (Eds.), *Learning, Arts, and the Brain: The Dana Consortium Report on Arts and Cognition* (pp. 17–49). Washington, DC: Dana Press. Retrieved from http://www.webmail.dana.org/uploadedFiles/News_and_Publications/Special_Publications/Learning, Arts and the Brain_ArtsAndCognition_Compl.pdf#page=27
Spence, S. A., Hunter, M. D., Farrow, T. F. D., Green, R. D., Leung, D. H., Hughes, C. J., & Ganesan, V. (2004). A cognitive neurobiological account of deception: evidence from functional neuroimaging. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *359*(1451), 1755–1762. https://doi.org/10.1098/rstb.2004.1555
Sperry, R. W., Gazzaniga, M. S., & Bogen, J. E. (1969). Interhemispheric relationships: the neocortical commissures; syndromes of hemisphere disconnection. In P. J. Vinken & G. W. Bruyn (Eds.), *Handbook of Clinical Neurology* (Vol. 4, pp. 273–290). Amsterdam: North-Holland. https://doi.org/10.1023/B:HUMP.0000036333.34541.54
Spiers, P. A. (1987). Acalculia revisited: Current issues. In G. Deloche & X. Seron (Eds.), *Mathematical Disabilities: A Cognitive Neuropsychological Perspective* (pp. 1–25). Hillsdale, NJ: Lawrence Erlbaum Associates.
Spinella, M., Yang, B., & Lester, D. (2007). Prefrontal systems in nancial processing. *Journal of Socio-Economics*, *36*(3), 480–489. https://doi.org/10.1016/j.socec.2006.12.008
Spinella, M., Yang, B., & Lester, D. (2009). Development of the Executive Personal Finance Scale. *The*

International Journal of Neuroscience, *117*(3), 301–313. https://doi.org/10.1080/00207450500534043
Spinnler, H., & Tognoni, G. (1987). Standardizzazione taratura italiana dei test neuropsicologici. *The Italian Journal of Neurological Sciences*, *Suppl. 8*, 1–120.
St George, M., Kutas, M., Martinez, A., & Sereno, M. I. (1999). Semantic integration in reading: Engagement of the right hemisphere during discourse processing. *Brain*, *122*(7), 1317–1325. https://doi.org/10.1093/brain/122.7.1317
Stoeckel, L. E., Stewart, C. C., Griffith, H. R., Triebel, K., Okonkwo, O. C., Den Hollander, J. A., … Marson, D. C. (2013). MRI volume of the medial frontal cortex predicts financial capacity in patients with mild Alzheimer's disease. *Brain Imaging and Behavior*, *7*(3), 282–292. https://doi.org/http://dx.doi.org/10.1007/s11682-013-9226-3
Strauss, E., Sherman, E. M., & Spreen, O. (2006). *A compendium of neuropsychological tests: administration, norms, and commentary* (3rd ed.). New York: Oxford University Press.
Tamura, I., Kikuchi, S., Otsuki, M., Kitagawa, M., & Tashiro, K. (2003). Deficits of working memory during mental calculation in patients with Parkinson's disease. *Journal of the Neurological Sciences*, *209*(1–2), 19–23. https://doi.org/10.1016/S0022-510X(02)00457-4
Triebel, K., Martin, R. C., Griffith, H. R., Marceaux, J., Okonkwo, O. C., Harrell, L., … Marson, D. C. (2009). Declining financial capacity in mild cognitive impairment: A 1-year longitudinal study. *Neurology*, *73*(12), 928–934. https://doi.org/10.1212/WNL.0b013e3181b87971
Trudeau, F., & Shephard, R. J. (2008). Physical education, school physical activity, school sports and academic performance. *The International Journal of Behavioral Nutrition and Physical Activity*, *5*(1), 10. https://doi.org/10.1186/1479-5868-5-10
Tudge, J. R. H., & Doucet, F. (2004). Early mathematical experiences: Observing young black and white children's everyday activities. *Early Childhood Research Quarterly*, *19*(1), 21–39. https://doi.org/10.1016/j.ecresq.2004.01.007
Turkheimer, E., Haley, A., Waldron, M., D'Onofrio, B., & Gottesman, I. I. (2003). Socioeconomic status modifies heritability of IQ in young children. *Psychological Science*, *14*(6), 623–628. https://doi.org/10.1046/j.0956-7976.2003.psci_1475.x
Uttner, I., Wahlländer-Danek, U., & Danek, A. (2003). [Cognitive Impairment in Adults with Neurofibromatosis Type 1]. *Fortschritte der Neurologie Psychiatrie*, *71*(3), 157–162. https://doi.org/10.1055/s-2003-37759
Vallar, G., & Perani, D. (1986). The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. *Neuropsychologia*, *24*(5), 609–622. https://doi.org/10.1016/0028-3932(86)90001-1
van Luit, J. E., van de Rijt, B. A., & Pennings, A. H. (1994). *Utrecht Early Numeracy Test*. Doetinchem: Graviant.
Varnhagen, C. K., Lewin, S., Das, J. P., Bowen, P., Ma, K., & Klimek, M. (1988). Neurofibromatosis and psychological processes. *Journal of Developmental and Behavioral Pediatrics*, *9*(5), 257–265.
Venneri, A., & Semenza, C. (2011). On the dependency of division on multiplication: Selective loss for conceptual knowledge of multiplication. *Neuropsychologia*, *49*(13), 3629–3635. https://doi.org/10.1016/j.neuropsychologia.2011.09.017
Vestergaard, M., Madsen, K. S., Baare, W. F., Skimminge, A., Ejersbo, L. R., Ramsoy, T. Z., … Jernigan, T. L. (2011). White Matter Microstructure in Superior Longitudinal Fasciculus Associated with Spatial Working Memory Performance in Children. *Journal of Cognitive Neuroscience*, *23*(9), 2135–2146. https://doi.org/10.1162/jocn.2010.21592
Vuilleumier, P., Ortigue, S., & Brugger, P. (2004). The Number Space and Neglect. *Cortex*, *40*(2), 399–410. https://doi.org/10.1016/S0010-9452(08)70134-5
Wadley, V. G., Harrell, L. E., & Marson, D. C. (2003). Self- and Informant Report of Financial Abilities in Patients with Alzheimer's Disease: Reliable and Valid? *Journal of the American Geriatrics Society*, *51*(11), 1621–1626. https://doi.org/10.1046/j.1532-5415.2003.51514.x
Ward, J. (2015). *The Student's Guide to Cognitive Neuroscience* (3rd ed.). London: Psychology Press.
Warrington, E. K., & James, M. (1967). Tachistoscopic number estimation in patients with unilateral cerebral lesions. *Journal of Neurology, Neurosurgery & Psychiatry*, *30*(5), 468–474. https://doi.org/10.1136/jnnp.30.5.468
Webber, L. S., Reeve, R. a, Kershaw, M. M., & Charlton, J. L. (2002). Assessing Financial Competence. *Psychiatry, Psychology and Law*, *9*(January 2015), 248–256. https://doi.org/10.1375/pplt.2002.9.2.248
Widera, E., Steenpass, V., Marson, D. C., & Sudore, R. (2011). Finances in the Older Patient With Cognitive

Impairment: “He Didn’t Want Me to Take Over.” *Jama*, *305*(7), 698–706. https://doi.org/10.1001/jama.2011.164

Willmes, K. (2008). Acalculia. In M. J. Aminoff, F. Boller, D. F. Swaab, G. Goldenberg, & B. L. Miller (Eds.), *Handbook of Clinical Neurology* (Vol. 88, pp. 339–358). Amsterdam: Elsevier,Science Ltd. https://doi.org/10.1016/S0072-9752(07)88017-1

Wilson, B. A., Cockburn, J., & Halligan, P. W. (1987). *Behavioural Inattention Test*. Bury St. Edmunds, UK: Thames Valley Test Company.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., … Petersen, R. C. (2004). Mild cognitive impairment - Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. In *Journal of Internal Medicine* (Vol. 256, pp. 240–246). Blackwell Science Ltd. https://doi.org/10.1111/j.1365-2796.2004.01380.x

Yu, X., Chen, C., Pu, S., Wu, C., Li, Y., Jiang, T., & Zhou, X. (2011). Dissociation of subtraction and multiplication in the right parietal cortex: Evidence from intraoperative cortical electrostimulation. *Neuropsychologia*, *49*(10), 2889–2895. https://doi.org/10.1016/j.neuropsychologia.2011.06.015

Zago, L., Pesenti, M., Mellet, E., Crivello, F., Mazoyer, B., & Tzourio-Mazoyer, N. (2001). Neural correlates of simple and complex mental calculation. *NeuroImage*, *13*(2), 314–327. https://doi.org/10.1006/nimg.2000.0697

Zamarian, L., Bodner, T., Revkin, S. K., Benke, T., Boesch, S., Donnemiller, E., & Delazer, M. (2009). Numerical deficits in a single case of basal ganglia dysfunction. *Neurocase*, *15*(5), 390–404. https://doi.org/10.1080/13554790902849156

Zamarian, L., Granà, A., Semenza, C., & Girelli, L. (2007). Rappresentarsi il “nulla”. Indagine sul concetto di “zero” in bambini di cinque e sei anni. In *Giornale italiano di psicologia* (Vol. 34, pp. 427–450). Bologna: Il Mulino. https://doi.org/10.1421/24630

Zamarian, L., Semenza, C., Domahs, F., Benke, T., & Delazer, M. (2007). Alzheimer’s disease and mild cognitive impairment: Effects of shifting and interference in simple arithmetic. *Journal of the Neurological Sciences*, *263*(1–2), 79–88. https://doi.org/10.1016/j.jns.2007.06.005

Zamarian, L., Stadelmann, E., Nürk, H. C., Gamboz, N., Marksteiner, J., & Delazer, M. (2007). Effects of age and mild cognitive impairment on direct and indirect access to arithmetic knowledge. *Neuropsychologia*, *45*(7), 1511–1521. https://doi.org/10.1016/j.neuropsychologia.2006.11.012

Zamarian, L., Visani, P., Delazer, M., Seppi, K., Mair, K. J., Diem, A., … Benke, T. (2006). Parkinson’s disease and arithmetics: The role of executive functions. *Journal of the Neurological Sciences*, *248*(1–2), 124–130. https://doi.org/10.1016/j.jns.2006.05.037

Zöller, M. E. T., Rembeck, B., & Bäckman, L. (1997). Neuropsychological deficits in adults with Neurofibromatosis type 1. *Acta Neurologica Scandinavica*, *95*(4), 225–232. https://doi.org/10.1111/j.1600-0404.1997.tb00103.x

Zorzi, M., Priftis, K., & Umiltà, C. (2002). Brain damage: neglect disrupts the mental number line. *Nature*, *417*(6885), 138–139. https://doi.org/10.1038/417138a

APPENDICIES

Appendix A: NADL Battery

NUMERICAL ACTIVITIES OF DAILY LIVING

(NADL)

IMPORTANT: This is only a short version of the battery as an example. For further information please visit http://journal.frontiersin.org/article/10.3389/fnagi.2014.00112/full)

Interview with patient

General	
Do you get confused by numbers	/1
Time	
Are you typically punctual for appointments	/1
Measure	
Do you administer your own drugs	/1
Money	
Do you shop by yourself	/1
Do you give the right money, get the right change	/2
Do you check your bank account	/1
Transportation	
Can you take the correct train/bus unaided	/1
Communication	
Do you make your own telephone calls unaided (i.e. do you dial them yourself)	/1
Can you select TV channels correctly	/1
Total	**/10**

Interview with caregiver

General	
Does s/he get confused by numbers	/1
Time	
Is s/he typically punctual for appointments	/1
Measure	
Does s/he administer her/his own drugs	/1
Money	
Does s/he shop by yourself	/1
Does s/he give the right money, get the right change	/2
Does s/he check her/his bank account	/1
Transportation	
Can s/he take the correct train/bus unaided	/1
Communication	
Does s/he make her/his telephone calls unaided (i.e. does s/he dial them yourself)	/1
Can s/he select TV channels correctly	/1
Total	**/10**

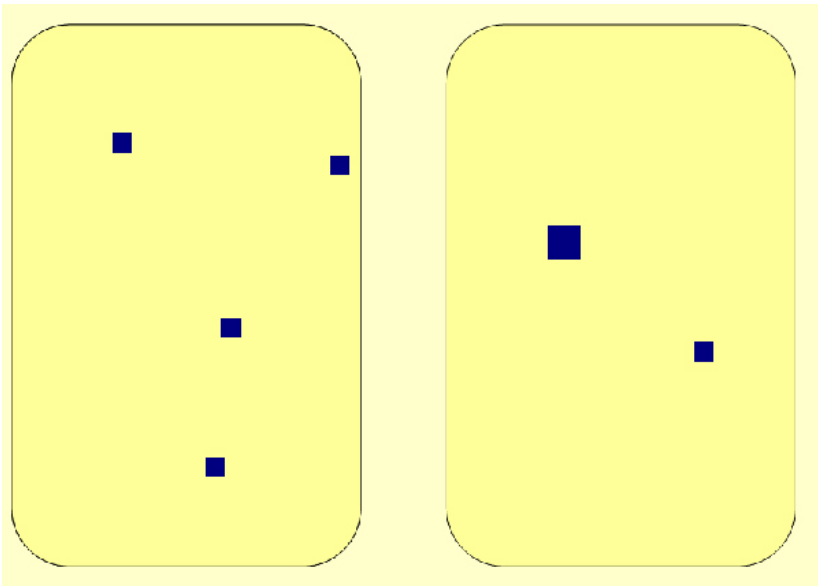
Informal test of numerical competence

Time	**Exact/reasonable answer**
Current time – (±15 min)	/1
Current day, year - exact	/2
How long have you waited? or How long are we speaking? (± 15 min)	/1
How long till 12 (if morning)/ 5 (if afternoon) (within ± 15 mins.)	/1
Measure	
How much pasta/rice for each person (80 g ±50)- reasonable	/1
Transportation	
Distance in km between home and hospital - reasonable	/1
Communication	
What is your telephone number? - exact	/1
General knowledge	
Age - exact	/1
Date of birth	/1
House number - exact	/1
Days of week/months in year - exact	/2
Dates of last war/attack on twin towers - exact	/2
Money	
How much is a new car (€7000-100000)	/1
How much is a house (€100000-2m)	/1
If a shirt normally costs €50, but is reduced by 10% how much will you have to pay? – (45) exact	/1
Coin usage	
Pay for newspaper (€1.2) given €1 and €2. Correct=Give €2	/1
Check change (60c). Correct=Say incorrect	/1
Say correct change (80c) or additional change (20c)	/1
Give correct money (€5.50) given 2, 2, 2, 1, 1, 1, 50c, 50c, 50c. If 2,2,1, 50c	/2
If correct in any other combination	*/1*
Total	**/23**

Formal assessment

Numerosity comparison test

Practice item *(example)*



Number line test

Practice item *(example)*

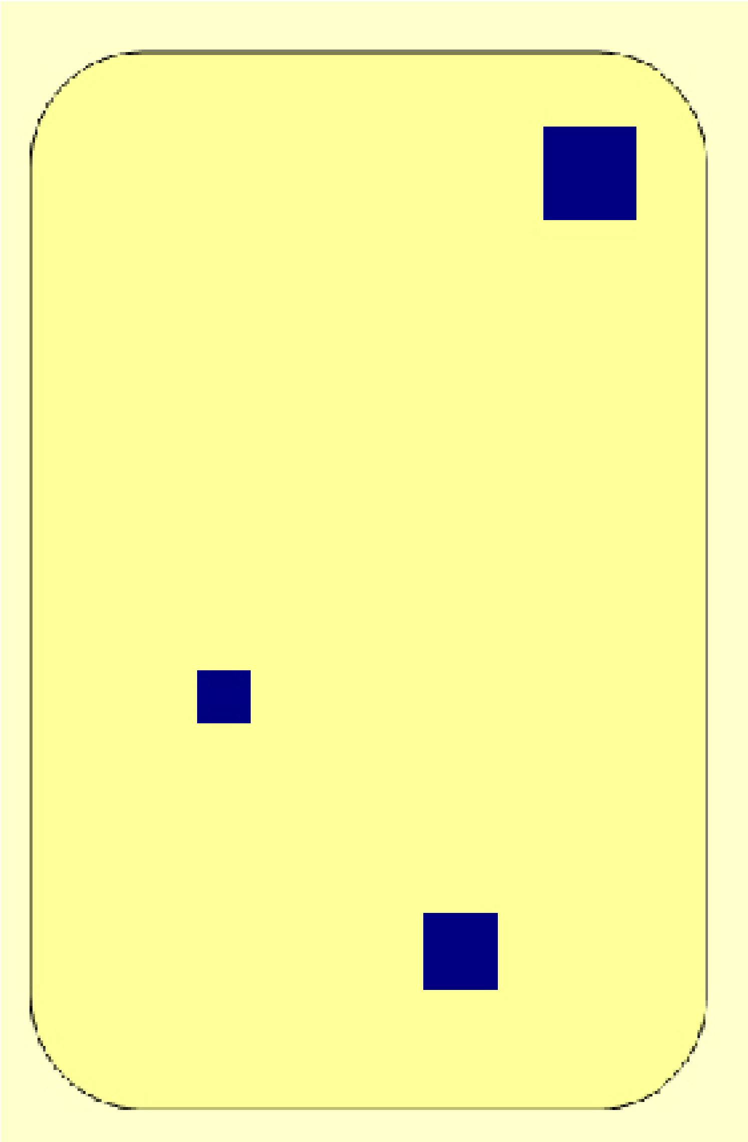
3

1 **10**

Digit comprehension test

Point to the digit corresponding to the number of squares

Practice item *(example)*



1 2 3 4 5 6 7 8 9 10

Score Sheets

A. NUMBER COMPREHENSION

1. Numerosity comparison

Question: Which panel has more squares?

Practice

Item	Congruency & difference	Answer	Score
1	C(ongruent) 2	R	
2	C 3	R	
3	I 1	L	
4	I 2	R	
5	C 1	L	
6	I 3	L	
Total			**/6**

2. Number line task (deviations in mm)

Practice 3

0-10	
5	
2	
7	
Total deviation in mm	
0-100	
50	
25	
75	
Total deviation in mm	
0-1000	
250	
750	
125	
Total deviation in mm	
Total	**/3**

3. Digit comprehension

Digit	Score
5	
4	
2	
8	
6	
9	
9	
8	
7	
6	
Total	**/10**

A. Total number comprehension: /19

B. READING AND WRITING NUMBERS

4. Reading Arabic numerals

Practice 4

Question	Score
12	
53	
104	
2600	
65300	
Total	**/5**

Errors

Lexical

Syntactic

5. Writing Arabic numerals to dictation

Practice 4

Question	Score
2	
51	
307	
2005	
42300	
Total	**/5**

Errors

Lexical

Syntactic

B. Total reading and writing numbers: /10

C. MENTAL CALCULATION

6. Mental calculation–Oral presentation

Question	Answer	Score
Practice1+6	7	
2+3	5	
5+2	7	
2+1	3	
7+7	14	
5+7	12	
9+6	15	
Addition Total		**/6**

Question	Answer	Score
Practice 7-3	4	
2-1	1	
9-6	3	
6-2	4	
16-8	8	
13-4	9	
11-4	7	
Subtraction Total		**/6**

Question	Answer	Score
Practice 5x3	15	
8x2	16	
5x6	30	
3x9	27	
8x7	56	
9x6	54	
8x9	72	
Multiplication Total		**/6**

C. Total mental calculation: /18

D. WRITTEN CALCULATION

7. Understanding arithmetical rules and principles

Rules

Question and answer	Answer	Score
0+9=	9	
7+0=	7	
7-0=	7	
3-3=	0	
0x7=	0	
1x6=	6	
4x0=	0	
Total rules		**/7**

Principles

Question	Answer	Score
Practice 42+19 = 61 → 19+42 =	61	
26+37 = 63 → 37+26 =	63	
68+43 = 111 → 111-43 =	68	
37+18 = 55 → 370+180 =	550	
60+29 = 89 → 61+29 =	90	
Total addition		**/4**

Question	Answer	Score
Practice 22x31 = 682 → 31x22 =	682	
56x17 = 952 → 17X56 =	952	
34x6 = 204 → 204÷6 =	34	
64x5 = 320 → 64+64+64+64+64=	320	
94x5 = 470 → 93x5=	465	
Total multiplication		**/4**

D. Total Written Calculation: /15

8. Written operations

Written addition

Question	Answer	Score
43+52	95	
657+231	888	
749+120	869	
58+43	101	
463+659	1122	
825+287	1112	
Total addition		**/6**

Written subtraction

Question	Answer	Score
79-34	45	
548-231	317	
456-132	324	
62-18	44	
317-126	191	
632-278	354	
Total subtraction		**/6**

Written multiplication

Question	Answer	Score
54x2=108	108	
25x8=200	200	
34x16=544	544	
429x53=22737	22737	
618x203=125454	125454	
Total Multiplication		**/5**

Total Written Operations: /17

Appendix B: NADL–F Battery

NADL–FINANCIAL

(english translation)

<u>Introduction</u>

Numerical Activities of Daily Living–Financial (NADL–F) is a novel battery that assesses the abilities to deal with money transactions in everyday life, with family- and self-finances, and with financial decisions. NADL–F is divided into seven domains; each domain evaluates the performance in ecological situations and focuses on activities that conceivably involve more than one cognitive function. NADL–F ultimately provides a standard and validated measure of independence to manage money, which in turn should contribute to the cognitive assessment in legal matters and to better delineate specific rehabilitation programs for clinical populations.

<u>IMPORTANT: This protocol reports a literal translation of the Italian version of NADL–F. This version of NADL–F is not meant to be used before adaptation.</u>

NADL–FINANCIAL

Domains

A. Counting Currencies

It requires the person to count money given (as when one receives the change) and to give money (as when one pays something).

B. Reading Abilities

It assess the person’s ability to properly read written numbers in everyday situations (e.g. prices, checks, bills, etc.) and to use this information to verify other people’s (e.g. cashers, waiters, etc.) behaviour.

C. Item Purchase

In each situation the examiner provides the person with cash and asks him/her to pay specific items with the money available/remaining, and to choose the most convenient item among a number of options (as it might happen in a shop).

D. Percentages

It requires the person to calculate percentages in ecological (e.g. in sales) situations.

E. Financial Concepts

This domain evaluates the person’s knowledge of the main and most frequently used financial concepts (e.g. taxes, interest, bank account).

F. Bill Payments

It assesses the ability to recognize, organize and effectively pay family bills (e.g. electricity, gas, etc.).

G. Financial Judgments

It evaluates the person’s capacity to judge whether a given decision could be beneficial or detrimental in economical terms. It also assesses the recognition of potential frauds.

NADL–FINANCIAL

General Instructions

1. Preparation

1.1. Before administering the test, the evaluator needs to be familiar with all the instructions, the material, the tasks, and the way of registering and scoring the answers. Therefore it is recommended to read through the instructions and the test a couple of times, and to carry out a pilot administration. The instructions could be learnt by heart, but it is advisable to hold the manual within reach.

1.2. The battery needs to be administered in a quite room where disturbing factors (for example telephone, noises from outside, etc.) are reduced to a minimum.

1.3. The examiner must Keep the test material, the instructions, the scoring form, work papers and pencil within reach. The materials should be given to the participant only when needed for a task to avoid distraction.

2. Administration

2.1. In this manual the instructions for the participant are written *in italics*, whereas the instructions for the evaluator are [within square brackets].

3. Scoring

3.1. The scoring is indicated at the end of each task.

3.2. No feedback should be given to the participant.

3.3. In case of spontaneous auto correction, the answer should be considered correct.

3.4. If it is clear that the person did not understand (or forgot) the question, the evaluator is allowed to repeat the instructions. In this case it should be indicated in the Comments for later analyses.

3.5. The Comments section could be used also to indicate the strategy used by the participant, the questions raised, or the behaviour (for instance distracted, stressed, worried, etc.).

3.6. In case the answer is wrong, it is recommended to write down the response given by the participant. This information is important to evaluate the cognitive state of the participant and to perform a qualitative analysis of errors.

A. Counting Currencies

Material:

Pack 1: €10, €5, €2, 50c, 20c, 10c.

Pack 2: €10, €2, €1, 20c (two), 5c.

Pack 3: €20 (two), €10, €5, €2, €1, 50c, 10c, 5c.

A.1. *I will give you some money; you should count it and tell me how much money I am giving to you.* [Give Pack 1: **€17,80**, then Pack 2: **€13,4**]. Scoring: 1 point for each correct answer.

A.2. [Give Pack 3: **€58,65**]. *Could you please give me **€45** from the money I just gave you? Now give me please **€12,60;** and finally **€18,65*** [replace the money back in the pack each time the person gives the amount requested; follow always the same order]. Scoring: 1 point for each correct answer.

B. Reading Abilities

Material:

- €107 bank check
- €30018 bank check
- €682 bank check
- €2050 bank check
- €78 restaurant bill
- Supermarket receipt

B.1. *You are about to receive a bank check. Could you please verify what is the amount of money written on it?* [show the €107 check]. Scoring: **1 point**.

B.2. *And what is the amount of money written on this bank check?* [show the €682 check]. Scoring: 1 point

B.3. *Here it is a bank check partially filled by now. Could you please verify whether the filled sections are correct?* [show the €30018 check]. Scoring: **1 point** if the answer is **NO**.

B.4. *Here it is abank check partially filled by now. Could you please verify whether the filled sections are correct?* [show the €2050 check]. Scoring: **1 point** if the answer is **YES**

B.5. *Imagine that you are in a restaurant and that you have to pay this bill* [show the €78 bill]. *You get to the cash desk and the cashier asks you to pay sixty-eight euros. Is that right?* [if the answer is NO, ask why]. Scoring: **1 point** if the answer is **NO** and the **explanation is correct**.

B.6. *Imagine that you went for shopping in the supermarket and got this receipt.* [show the supermarket receipt]. *Could you please check how much did you pay for the jam? And how much was the partially skimmed milk?* Scoring: **1 point** if **both** answers were **correct** [**1.55** for the jam and **1.20** for the milk].

B.7. *Now, could you please check whether the discount to the detergent was actually applied?* Scoring: **1 point** if says **NO**.

C. Item Purchase

Now we are going to simulate shopping situations. In each situation I would ask you to pay with the banknotes or coins which correspond or at least get close to the amount you have to pay. For example, if an object costs 5€ you should pay with the 5 note (if available), instead of using the 10 note.

Material:

Pack 4: 50c (three), 20c (two), 10c, 5c (two).

Pack 5: €2, €1.

Pack 6: €20, €10, €5

Pack 7: €5, €2 (two), €1 (two), 20c, 10c (two).

Pictures for multi-item shopping

1-item

C.1. [Give Pack 4] *Use this money to pay me a cup of coffee that costs 90 cents. Please take into consideration that I do not have change.* Scoring: **1 point**.

C.2. [Take all the money of Pack 4 and give it back to the person] *Could you please pay me also a cappuccino that costs €1,10.* Scoring: **1 point**.

C.3. [Give Pack 5] *From now on I can give you the change. Could you please pay me a bus ticket that costs €1,20*. Scoring: **1 point** if the person gives **€2**.

C.4. *How much change do I have to give you?* Scoring: **1 point** if the answer is **80 cents**.

C.5. [Give Pack 6] *Now please pay me a plant that costs €26.50.* Scoring: **1 point** if the person gives **€30**.

C.6. *How much change do I have to give you?* Scoring: **1 point** if the answer is **€3,50**.

Multi-item

C.7. *You get this money* [Give Pack 7] *because you need to buy a bottle of olive oil that costs €4,10 and 1Kg of tomatoes for €1,98. Could you give me the money to pay both items?* [Show the corresponding image and keep it in front of the person during the task]. Scoring: **1 point** if the amount > **€6,08**.

C.8. *How much change do I have to give you?* Scoring: **1 point** if the answer is correct.

C.9. [Give the Pack 7 money back] *Now you want to buy 1Kg of oranges for €1,70, 1 Kg of apples for €1,40 and some bananas for €1,20. Please pay me all the items.* [Show the corresponding image and keep it in front of the person during the task]. Scoring: **1 point** if the amount > **€4,30**.

C.10. *How much change do I have to give you?* Scoring: **1 point** if the answer is correct.

C.11. [Give the Pack 7 money back] *Now you get back to the supermarket because you want to* *buy 2 Kg of oranges and 2 Kg of bananas. How much money do you have to pay approximately?* Scoring: **1 point** if the answer is **between €5 and €7**.

C.12. *The actual amount to pay is €5.80. Pay it to me please.* Scoring: **1 point** if the answer is correct.

C.13. *How much change do I have to give you?* Scoring: **1 point** if the answer is correct.

C.14. *If one litter of milk costs 90 cents, how much would you have to pay for 12 litters? More or less than €11?* Scoring: **1 point** if the answer is **< €11**.

D. Percentages

D.1. *If a cell phone costs €100 minus 30% discount, how much should you actually pay for it?* Scoring: **1 point** if the answer is **€70**.

D.2. *If the price of a pair of shoes is* €70 *minus 10% discount. How much should you pay for it?* Scoring: **1 point** if the answer is **€63**.

D.3. *Imagine that you are about to buy a dress of* €50 that has 20% discount. *How much should you pay for it?* Scoring: **1 point** if the answer is **€40**.

D.4. *You need to buy a shirt for €50, when you get to the cash desk you read that if you get two shirts of the same style you get a 40% discount; so you decide to get the offer and buy the two. How much should you pay in total?* Scoring: **1 point** if the answer is **€60**.

D.5. *One person receives 3% interests over €1000. How much money is that?* Scoring: **1 point** if the answer is **€30**.

D.6. *Which one is cheaper: a mozzarella that costs €2* or another one that costs €3.50 with 20% discount? Scoring: **1 point** if the answer is the **second one**.

D.7. *Which one is cheaper: a refrigerator that costs €1200* with 20% discount or another one that costs €1000 without discount? Scoring: **1 point** if the answer is the **first one**.

D.8. *You decided to buy a sofa that costs €800 and chose to get a deal such that you will pay it in 10 equal instalments. In the last instalment you also will have to pay 5% interests over the initial price of the sofa. How much will the last instalment be?* Scoring: **1 point** if the answer is **€120**.

D.9. *Imagine that you bought a new bed in 4 monthly instalments. What is the percentage that remains to be paid after the first payment?* Scoring: **1 point** if the answer is **75%.**

E. Financial concepts

I will now ask you to define (say what is the meaning or the utility of) some terms. Scoring: 1 point if the definition includes one keyword, 2 points if it includes both keywords.

Concepts	Keywords
E.1. Taxes	Payment – State/government
E.2. Income	Money earn – a period of time
E.3. Bank account	Bank – Funds deposited
E.4. Interest	Money lent or debt – Percentage/rate
E.5. IBAN	Code – bank accounts/ transactions
E.6. Instalment	Payment – spread/divided in a period
E.7. ISEE (applies in Italy)	Economical situation – Family

F. Bill Payments

Material:

Bills with different payment dates.

Unbalanced bills

In daily life it is necessary to know how to manage and pay bills. These are some examples of bills that you can find in our country [show the material]; *now I will ask you some questions related to them.*

F.1. *Could you please define what a bill is?* Scoring: **1 point** if the answer includes these **two terms**: **Payment** and **Service**.

F.2. *Which are the most important house bills?* Scoring: **1 point** if the answer includes **at least three** of the following: **Electricity, water, gas, telephone, internet**.

F.3. *How much is the total amount due for this bill?* [show Bill 1]. Scoring: **1 point.**

F.4. *And what about this one? How much do you have to pay for this bill?* [show Bill 2]. Scoring: **1 point**

F.5. *Please organize these bills on the basis of the due payment dates.* Scoring: **1 point** if the arrangement is correct.

F.6. *Sometimes you see a positive balance in your bill. What does it mean?* Scoring: **1 point** if the definition includes these **two terms**:

payment/reimbursement/adjustment” – “**actual consumption**”.

G. Financial Judgments

G.1. *A person inherits €250,000. For a long time this person wanted to buy a house and finally he gets the chance to realize his dream. However, he decides to first spend €2,000 to buy a scooter, which would be very convenient to go to work.* Does it seem a reasonable choice to you? **FILLER**

G.2. *A person who really likes watches decides to buy one for his birthday. In order to gain the money necessary to buy it, he decides to sell his new refrigerator. Does it seem a reasonable choice to you?* **FILLER**

G.3. *A growing company has little money to invest, but a great need of manpower to be able to complete an important project. The director chooses to sell some machines to hire more workers. Does it seem a reasonable choice to you?* Scoring: **1 point** if the answer is **NO**

G.4. *A young manager has just been promoted. He knows for sure that, from now on and at least for the next 10 years he will earn € 5,000 per month. To celebrate the event, he decided to buy a new car, spending € 35.000. Does it seem a reasonable choice to you?* **FILLER**

G.5. *A technician from the electricity company came to read the meter. When he finished, he offers you the option of paying him the last bill. In this way you won't need to go to the bank/post office/bill payment centre yourself. Does it seem a reasonable choice to you?* Scoring: **1 point** if the answer is: **"It is a FRAUD".**

G.6. *A woman has so many financial problems that she can not even pay the fuel that her own car consumes. To solve her financial problems, she decides to buy a new, low fuel consumption car, that she will pay in instalments. Does it seem a reasonable choice to you?* **FILLER**

G.7. *A young man who is looking for a job has to decide between a lifetime job offer with a €2,000 salary per month, or a one-year contract with a salary of €3,000 per month. He decides to accept the €2,000 contract. Does it seem a reasonable choice to you?* **FILLER**

G.8. *You get a phone call from your bank. The agent proposes an investment to you: by investing €500 per year, you will earn up to €5,000 and not less than €2,000 at the end of the year. Would you accept to make the investment?* **FILLER**.

G.9. *A small family business had negative balances in the last six months. A bigger company offers to buy the small business, offering them the possibility to get out of the crisis. Moreover, the members of the family can continue working within the company. The family chooses to accept the offer. Does it seem a reasonable choice to you?* **FILLER**

G.10. *Personnel from the National Institute of Statistics has come to your house to help you filling the latest national survey. The person requests some money for the service but at the end decides to make you a discount because of your kindness. Does it seem reasonable?* Scoring: **1 point** if the answer is**: "It is a FRAUD".**

G.11. *A person receives a proposal from his new neighbour of lending him some money. The neighbour will use this money to pay a lawyer for a practice that will allow him to retrieve a large sum of money. The neighbour asks the person to invest €1000, offering then to get €10,000 back at the end of the process. The person accepts. Does it seem a reasonable choice to you?* Scoring: **1 point** if the answer is: **"It is a FRAUD".**

G.12. A woman has just lost her job. The only thing that remains to her are €10,000 in her bank account . To solve her economic problems, the woman decides to invest all her savings in the stock market in unsafe actions that might however make her earn a lot of money. *Does it seem a reasonable choice to you?* Scoring: **1 point** if the answer is **NO**.

G.13. *A very close friend of yours gets in contact to ask you a favour: he has financial problems and needs a loan of €1000. He promises to give you the money back as soon as possible. For you itis not a problem to lend this money. Would you lend the €1000 to him?* **FILLER**

G.14. *A person decides to give €20 for charity. People from the charity foundation tell him that the minimum contribution should be €50. Does it seem reasonable to you?* Scoring: **1 point** if the answer is: **"It is a FRAUD"**.

G.15. *An elderly woman who lives alone and has no children has difficulties to reach the end of the month receiving only €400 of pension.* An estate agency offers her this possibility: she will sell her house, but she can continue living there without paying any rent and she will additionally receive €2.000 per month. *The house will become property of the agency only after she dies. The lady accepts the proposal. Does it seem a reasonable choice to you?* **FILLER**

G.16. *You decide to buy a camera. You found an ad in the newspaper selling a one-year used camera of the model you like. While the new camera costs € 1500, the one you just saw in the advertisement costs €200. Would you buy it?* **FILLER**

G.17. *A person receives an offer from his bank concerning an investment. Investing €500 the person may lose them all or earn €200. The person accepts. Does it seem a reasonable choice to you?* **FILLER**

G.18. *A person lives in an apartment paying a monthly rent of €600. The person is quite happy with the apartment and hopes not to move out. The owner proposes him to buy the house. To have the money necessary for paying it, the person should request a 20 years loan and the amount of the monthly payment would be €600. The person decides to continue paying the rent. Does it seem a reasonable choice to you?* **FILLER**

NADL–F Interview

Now I will ask you some questions about your capability when using money and managing your finances. For each question, you should tell me if you are independent, if you are able to manage with some help, or if you not able to complete the task. Even if some questions may appear to be very simple, please carefully consider and answer all of them.

Name ________________________

Administration date _____________

	NO (0)	**Yes with help** (1)	**Yes** (2)
A. Counting Currencies			
A1. Are you able to count money when you have to pay something?			
A2. Are you able to count even the smallest coins?			
B. Reading Abilities			
B1. Are you able to read the price tags in a supermarket. And the amount reported on the supermarket bills?			
B2. Are you able to use checks?			
C. Item Purchase			
C.1 Are you able to shop in a supermarket?			
C.2 When you purchase something,are you able to count the change?			
D. Percentages			
D.1 If there are some products discounted by 30%, 40%, or 50%, are you able to calculate the discount?			
F. Bill Payments			
F.1 Are you currently involved in paying your bills? If not, would you be able to do it?			
G. Financial Judgments			
G.1 Are you able to make choices concerning important purchases, such as a new house or a new car?			
G.2 Are you able to make important economic choices, such as asking for a mortgage, or for a loan?			
G.3 Are you able to detect scams?			

Total Score (sum of Item scores) ______________

Appendix C: Zero in the brain: A voxel-based lesion-symptom mapping study in right hemisphere damaged patients

(Published in Cortex, 2016, Vol. 77)

C.1. Introduction

The starting point for this study is the present uncertainty about the specific role of the right hemisphere in number processing and calculation. Clinical studies, as well as more recent investigations conducted with other methodologies (e.g. neuroimaging, transcranial magnetic stimulation, direct cortical electro-stimulation) leave several unanswered questions about the contribution of the right hemisphere in this domain. From their study on split-brain patients, Sperry *et al.* argued that the right hemisphere's capacity for calculation is "almost negligible" (Sperry, Gazzaniga, & Bogen, 1969). Acalculia following a right-hemisphere lesion is however a common finding. When the right hemisphere is damaged, at least in certain areas, numerical abilities appear to be impaired in different ways (Ardila & Rosselli, 1994; Basso et al., 2000; Hécaen, 1962; Hécaen & Angelergues, 1961; Warrington & James, 1967). Since the earliest report from (Henschen, 1926), most studies seem just to have assumed that acalculia from a right-hemisphere lesion was secondary to spatial disorders or to a generalized reduction of cognitive resources (see, for reviews Hartje, 1987; Miceli & Capasso, 1999). A study by Grafman and colleagues (Grafman et al., 1982), however, concluded that, even if impairment of intelligence or visuo-constructive difficulties contributes to calculation disorders, right-hemisphere acalculia can still be partially independent of such disorders. These authors did not perform an error analysis and did not go further in suggesting what the right hemisphere does.

Trying to elucidate the role of the right hemisphere in number processing from the studies on crossed aphasia (in which the right hemisphere is the one holding language abilities) are even more problematic, because the numerical deficits are difficult to isolate from the linguistic ones. Indeed, a study by Semenza and collaborators on crossed aphasia reports that the type of acalculia observed in this group of patients is very much like that usually found in left-hemisphere lesions (Semenza et al., 2006).

Neuroimaging and neuropsychological approaches gave mixed results. While most studies (e.g., Dehaene & Cohen, 1995; Dehaene et al., 2003) emphasized the working of the left hemisphere in calculation, some recent investigations suggested that the right hemisphere might be involved even in simple calculation (Andres, Seron, & Olivier, 2007; Benavides-Varela et al., 2014). Evidence of relatively more intense activation in the right hemisphere seems to be related possibly to proficiency (Zago et al., 2001). Moreover, a meta-analysis conducted on functional MRI-based studies (Arsalidou & Taylor, 2011) found that activity is dominant in the right hemisphere for subtraction, and primarily in the right hemisphere for multiplication. Consistent with this last finding are relatively recent studies by (Rosenberg-Lee et al., 2011), as well as (Price et al., 2013).

Besides confirming the involvement of the left parietal areas (and in particular of the left angular gyrus), transcranial magnetic stimulation reports (e.g., Andres et al., 2011; Cohen Kadosh et al., 2007; Göbel et al., 2001; Salillas & Semenza, 2014; Salillas et al., 2012), also attribute some simple calculation functions to the right hemisphere, whereby parietal areas seem to be involved at least in simple multiplication.

Finally, direct cortical electro-stimulation performed during surgery on the right hemisphere (Della Puppa et al., 2013, 2015; Yu et al., 2011) provided evidence of positive sites for addition, multiplication, and subtraction in right parietal areas. Importantly, these positive sites were operation-specific: e.g., a site positive for addition was never positive for multiplication and vice versa. This finding suggests that the errors induced by cortical inhibition reflect the interruption of specific information processing in the right hemisphere rather than resulting from an unspecific shortening of processing resources.

The studies reviewed above suggest that investigating specific numerical abilities may provide a clearer idea about what the right hemisphere actually does. Along these lines, the present study addressed the issue of number transcoding, namely the process of transforming an Arabic number from a given representational format (e.g. phonological, forty) into another format (e.g. written numerals, 40). A task like reading aloud requires the transcoding of Arabic or alphabetically written numbers into spoken number words whereas writing to dictation involves the reverse transcoding process.

As in the case of other numerical tasks (see above), number transcoding impairments have been reported almost exclusively in left hemisphere-damaged patients (Deloche & Seron, 1982a, 1982b). Not surprisingly, the literature reports that most patients with transcoding deficits are also affected by aphasia or showed difficulties in writing or reading words (Delazer & Bartha, 2001; Delazer, Girelli, Semenza, & Denes, 1999).

Still, few neuropsychological studies have reported transcoding errors in right-hemisphere damaged patients (RHD), who do not show language deficits (Ardila & Rosselli, 1994; Basso et al., 2000; Furumoto, 2006; Priftis, Albanese, Meneghello, & Pitteri, 2013; Rosselli & Ardila, 1989), indicating that cognitive abilities other than language are also necessary for transcoding. However, the conclusions drawn on the actual abilities involved are not entirely consistent across studies. RHD patients' failure in transcoding has been attributed to disparate functions including spatial processing in general (Rosselli & Ardila, 1989), the spatial abilities involved in constructional apraxia, namely errors of spatial displacement and omissions in copying tasks (Basso et al., 2000), or "constructional place-holding-digit elaborations" of *zero* in the Japanese number system (Furumoto, 2006). This variety of interpretations has increased the uncertainty about the contribution of the right hemisphere. As a consequence, the idea that transcoding numbers relies on unilateral left-hemisphere networks still prevails in the literature (Cipolotti & van Harskamp, 2001; Semenza, 2008).

One way to understand the specific contributions of different brain areas to transcoding would be to capitalize on available theoretical frameworks and formal descriptions of the process. In the last decades, several cognitive models have been advanced in order to describe number transcoding. Some of these models assume an intermediary semantic representation between the input and the output code (McCloskey et al., 1985; Power & Dal Martello, 1990); whereas others argue that the process does not necessarily require semantic representations of the number, only asemantic production rules (Barrouillet, Camos, Perruchet, & Seron, 2004; Cipolotti, 1995; Cipolotti & Butterworth, 1995; Cohen, Dehaene, & Verstichel, 1994; Deloche & Seron, 1987; Power & Dal Martello, 1997).

Power and Dal Martello, for example, proposed influential semantic and asemantic models to explain the way transcoding takes place in developmental populations (Power & Dal Martello, 1990, 1997). Their model proposes a systematic – i.e. computable – process for turning a name-based verbal system of numerals into the familiar positional system with digits. For instance, according to their paper in 1990, a number such as *three thousand and sixty five* would activate a semantic[4] representation of the quantities associated to each power of ten: 3×10^3, 0×10^2, 6×10^1 and 5×10^0. This yields three terms 3000, 60 and 5. Subsequently, two rules or operators would be used to transform this representation into an Arabic number. The concatenation operator which applies only to tens and units, takes the number of units, in this case, 5 and concatenates it with the number of tens, in this case, 6, to give 65, in their formalism 6&5→65. For larger numbers this will not work. Consider *three thousand and five*: taking the number of thousands, 3 and concatenated with the number of units, 5, would yield 35; taking 3000 as a whole and concatenating with 5 - 3000&5 - would yield 30005, which is also incorrect. Therefore, they proposed the second rule, *overwriting*, in which the zeros in 3000 are overwritten from right by the number of digits generated by the units, tens, and/or hundreds. Hence in our example, the 65 in *three thousand and sixty five* overwrites the rightmost two zeros to yield the correct result, 3065: 3000#65→3065, where # is their symbol for overwriting. (Power & Dal Martello, 1990) showed that children learn the overwriting rule later than concatenation, because it is more complex, with children often writing large numbers such as in *three thousand and sixty five* as 300065, where they have mastered the concatenation rule but not

[4] The authors acknowledged, however, that their results had no bearing on the issue of whether the transcoding process is semantic or asemantic; they subsequently stated that an analogous explanation using asemantic rules could have also accounted for their data (Power & Dal Martello, 1997). For the purpose of this work, the focus should thus be on the operations and not the type of representations described in the model.

the overwriting rule. Notice that the problem for the child is specifically with numbers containing *zeros*, since it is only these that need to be overwritten.

The model of Power and Dal Martello has had great impact on later research. It has inspired and has proven compatible with phenomena observed not only in developmental populations (Lucangeli, Tressoldi, & Re, 2012; Seron, Deloche, & Noël, 1991; Seron & Fayol, 1994) but also in neuropsychological patients (Cipolotti et al., 1994; Granà et al., 2003). For example, the patient of (Cipolotti et al., 1994), who had a left-hemisphere lesion, transcoded *one thousand nine hundred and forty-five* as 1000,945, *three thousand two hundred as 3000,200, and twenty-four thousand one hundred and five* as 24000,105. He was able to concatenate correctly, and to use overwriting for 100s, but did not apply overwriting when it came to thousands. Incidentally, he was able to read long Arabic numbers correctly and used this spared ability to correct his transcoding errors within two days.

Despite the influence of the Power and Dal Martello's model, to date the brain areas underlying the processes described in it have not been established. Furthermore, the neuropsychological evidence gathered in favour of this model has not attempted to associate the anatomical and functional aspects of the patients' pattern of errors either.

The aim of the present study was thus to shed some light on the contributions of the right cerebral hemisphere to number transcoding, also in relation to a more specific localization of the various aspects of this function, and its putative operations. A comprehensive qualitative analysis of errors was implemented with the aim of associating different error categories with specific cognitive functions and brain regions. Particular focus was given to digits containing *zeros*, whose properties are fundamental for the completion of the transcoding operations described by Power and Dal Martello in their model.

Zeros are generally problematic in calculations(Pesenti, Depoorter, & Seron, 2000; Semenza et al., 2006), mental representations (Merritt & Brannon, 2013; Zamarian, Granà, Semenza, & Girelli, 2007) and transcoding between different number codes (Cipolotti et al., 1994; Granà et al., 2003;

Noël & Seron, 1995; Power & Dal Martello, 1990; Seron & Fayol, 1994). We hypothesized that representing and processing *zeros* would be particularly difficult for right-hemisphere damaged patients performing transcoding tasks for at least two reasons. First, when functioning as a placeholder (e.g. 2014), *zero* is generally not expressed in the verbal code of most languages (Mandarin Chinese is an exception). Thus, its temporary representation in a hypothetical buffer, most likely depends upon visuo-spatial processes, typically impaired in RHD patients. Second, transcoding, and in particular the overwriting operation, relies upon the capacity to merge the information derived from a previous intermediary process of transcoding (i.e. 2000#(10&4) → 2014). This integrative function that allows people to achieve global coherence has been associated also to right-hemisphere brain areas (St George, Kutas, Martinez, & Sereno, 1999).

C.2. Materials and methods

C.2.1. Participants

22 RHD patients (N = 14 males; mean age = 59.00 years, SD = 12.59; range: 38-77; mean education = 11.64 years, SD = 3.84; range: 5-18) participated in the present study. Inclusion criteria were absence of dementia, substance abuse, and psychiatric disorders. Moreover, in order to exclude cognitive impairment, all patients underwent assessment of global cognitive functions with the Mini Mental State Examination (MMSE) test (Magni et al., 1996). All patients were right-handed and had unilateral right-hemisphere lesions. Demographic and clinical data are reported in Supplementary Material 8. A control group of 20 participants (N = 10 females; mean age = 63.05 years, SD = 8.87; range: 39-78; mean education = 11.65 years, SD = 4.14; range: 5-22) with no history of neurological or psychiatric illness was also tested. There were no significant differences between the group of patients and the control group in age $\chi^2(1)$ =.83, p = .41, education $\chi^2(1)$ = -.13, p = .90, and gender distribution Z = .89, p = .37. Differences between patients and controls were found in the MMSE scores $\chi^2(1)$ = 3.56, p < .001. The data of all participants were collected in

accordance with the Helsinki Declaration II and the Institutional Ethics Committee of the IRCCS San Camillo Hospital Foundation, Lido-Venice, Italy.

C.2.2. Transcoding tasks

Two transcoding tasks were presented to the participants: reading Arabic numerals and writing to dictation in the Arabic code. The tasks included 1 to 6-digit numerals. In the reading task, a set of 120 items was used, 88 of which contained at least one zero. In the writing task, 72 items were presented: 52 items contained *zero* (a full list of the items used is reported in Supplementary Material 8). In both tasks the stimuli were presented in random sequence.

C.2.3. Supplementary numerical tasks

To further evaluate the implication of spatial processing in transcoding tasks, two supplementary tests were administered and correlated with participants' performance. The first one measured minimal visual-spatial and motor coordination abilities required to read and write numerals. It consisted of copying Arabic numerals. The task included 16 items varying from 2 to 6-digits. Half of the items contained at least one *zero*.

In the second task, participants were requested to spell the digits composing an orally presented number. For instance *centotrentadue* (translated to *one hundred and thirty two*, in English) should be correctly spelled like *one-three-two*. This task employs representational abilities similar to those required in transcoding, yet importantly, as opposed to the previous supplementary task it did not rely on the patients' abilities to process the visual input or on their motor abilities. Moreover, it did not involve any syntactic rules for combining the single digits and thus allowed for isolating effects related to those rules. The test consisted of 18 items ranging from 2 to 6 digits; half of the items contained *zeros*.

C.2.4. Statistical Analysis of Behavioural data

The comparison between the performance of healthy control participants and patients was carried out using the non-parametric Wilcoxon rank sum test. This test was chosen because of the lack of homogeneity of variance between groups as measured with Bartlett multiple-sample test (writing $\chi^2(1) = 40.59$; $p < .001$; reading $\chi^2(1) = 7.73$; $p < .005$; spelling $\chi^2(1) = 11.51$; $p < .001$) and also because the data were not normally distributed (Kolmogorov-Smirnov test for writing $D = .62$, $p < .001$; reading $D = .48$, $p < .01$; copying $D = .77$, $p < .001$; spelling $D = .44$, $p < .05$). In the transcoding tasks, the effects of item length and number of *zeros* were evaluated using ANOVAs across items. Post-hoc comparisons among different item-lengths (1,2,3,4,5,6-digits items) and number of *zeros* (0,1,2,3,4 *zeros*) underwent Bonferroni's correction for multiple comparisons.

Additional analysis were carried out within the reading task by choosing A) all the items with two repeated digits positioned next to each other (i.e. 1333, 4114, 8843, 3655, 43766, 45322, 61211) and pairing them with B) randomly chosen items of the same length and similar repetition structure instantiated over *zeros* (i.e. 7200, 1003, 4002, 9900, 70013, 98001, 61700), and C) randomly chosen items of the same length containing only one *zero* (i.e. 7089, 5630, 1089, 9204, 57802, 71230, 74083).

The number of errors in B and C was representative and did not differ statistically from the whole pool of items of their same size and structure (both *p*s > .05). A non-parametric Wilcoxon rank sum test was then used to compare the number of patients erring items in A with the number of patients erring items in B and in C.

C.2.5. Qualitative coding

Errors were generally classified as involving *zeros* or not. Moreover, each category was subdivided according to whether it implied the addition of digits, omissions, or lexical errors (see **Table C.1** for examples of the patients' errors). *Zero* errors that corresponded to a failure applying the overwriting rule described in the introduction (Power & Dal Martello, 1990), were coded separately. There were two additional errors in the reading task: the consecutive use of the multiplicand (see Power & Dal Martello, 1997), e.g. 209000 → *duemila novemila* (in English *two thousand nine thousand*); and fragmented reading (Seron & Deloche, 1983). The latter included grouping strategies of one digit: e.g. 106 → *uno zero sei* (in English *one zero six*), two digits: e.g. 683612 → *sessantotto trentasei dodici* (in English *sixty-eight thirty-six twelve*), three digits: e.g. 800700 → *ottocento settecento* (in English *eight hundred seven hundred*), four digit grouping, and a mix of the above (e.g. 916072 → *novantun mila seicento sette due* (in English *ninety one thousand six hundred seven and two*).

C.2.6. Regression Analysis

In order to determine the role of cognitive abilities underlying the errors, we performed separate stepwise regressions over the absolute frequency of each error type and including the following measures as predictors: *a. Neglect assessment* which includes the sum of the following subtests of the Behavioural Inattention Test part Conventional (BIT-C; Wilson et al., 1987): line crossing, letter cancellation, star cancellation, line bisection; *b. Executive functions* (i.e. the phonemic verbal fluency test); *c. Short term memory* (i.e. digit span forward); *d. Working memory* (i.e. digit span backward); *e. Attention* (i.e digit cancellation test as in attentional matrices); and *f. Representational Visuo-spatial abilities* including the sum of the patients' scores on two BIT-C subtests: figure and shape copying and representational drawing. Diagnostic tests performed separately for each model indicated a Cook's distance > 1 in PZ_8 for "Omission of *zeros*". This patient was thus excluded from the calculation of the model. Additional regression analyses were performed with data from all participants, including age, MMSE, and education as predictors.

Table C.1 | Examples of patients' responses and their categorization.

Type of error	Reading		Writing	
	Item presented	Patient's response	Item presented	Patient's response
Over-writing rule failure	70002	seven thousand and two three hundred	ten thousand seven hundred and fifty seven	310000757
Addition of zeros	30040	three hundred thousand and forty	ten thousand and fifty	100050
Addition of digits (no zero)	683612	one million six hundred eighty-three thousand six hundred and twelve	eight	18
Omissions of zeros	543006	fifty-four thousand three hundred and six	one hundred thousand and three	10003
Omission of digits (no zero)	24006	four thousand and six	seven hundred eighty-nine thousand six hundred and thirty-four	780000
Semantic errors involving zero	107538	one hundred seventy-five thousand and thirty-eight	nine hundred eight thousand and four	900804
Semantic errors not involving zero	1367	three thousand three hundred and sixty-seven	sixty thousand and forty	70 040
Fragmentation	789634	seven hundred and eighty-nine six hundred and thirty-four	—	—
Fragmentation involving "zero"	70006	seventy thousand zero zero six	—	—
Consecutive multiplicand	209000	twenty thousand nine thousand	—	—

C.2.7. Voxel-based lesion–symptom mapping analysis

For all patients, CT, MRI T1 and/or T2-weighted scans were used to determine lesion location. Lesions were drawn on axial slices of a T1-weighted template using the MRIcron software package (Rorden & Brett, 2000). The lesion was mapped onto each single slice where the lesion was present (slice thickness = 1mm). An experienced neuroradiologist, who was blind to the purpose of the study, defined the lesion extensions.

The voxel-based lesion-symptom mapping (VLSM) technique (Bates et al., 2003; Rorden et al., 2007) was implemented using the nonparametric mapping (NPM) software that is distributed as part of the MRIcron toolset. Specifically, the nonparametric Liebermeister test was applied to identify voxels that, when injured, predicted the presence of a specific transcoding error. To minimize possible outlier effects, the analyses were conducted only on voxels damaged in at least 2 patients (442081 voxels out of 7109137; about 6.2% of voxels). The resulting statistical map was adjusted for multiple comparisons by using False Discovery Rate correction $p < 0.01$. See also the Supplementary Material 8 showing the general pattern of lesion overlap.

The binomial distribution that was used for the design matrix on the NPM was defined using iterative cluster analysis. Behavioural data from patients and controls were included in the analysis in order to objectively divide patients whose performance was comparable to that of controls from patients with abnormal frequency of a specific error type. The analysis employed a sum of absolute differences as the distance measure, as implemented in the city block parameter of Matlab. In this way, the centroid of each cluster was the component-wise median of the points in that cluster. The clustering was iterated 100.000 times, each with a new set of initial cluster centroid positions. The solution with the lowest value of the within-cluster sums of point-to-cluster-centroid distances was then selected.

C.3. RESULTS

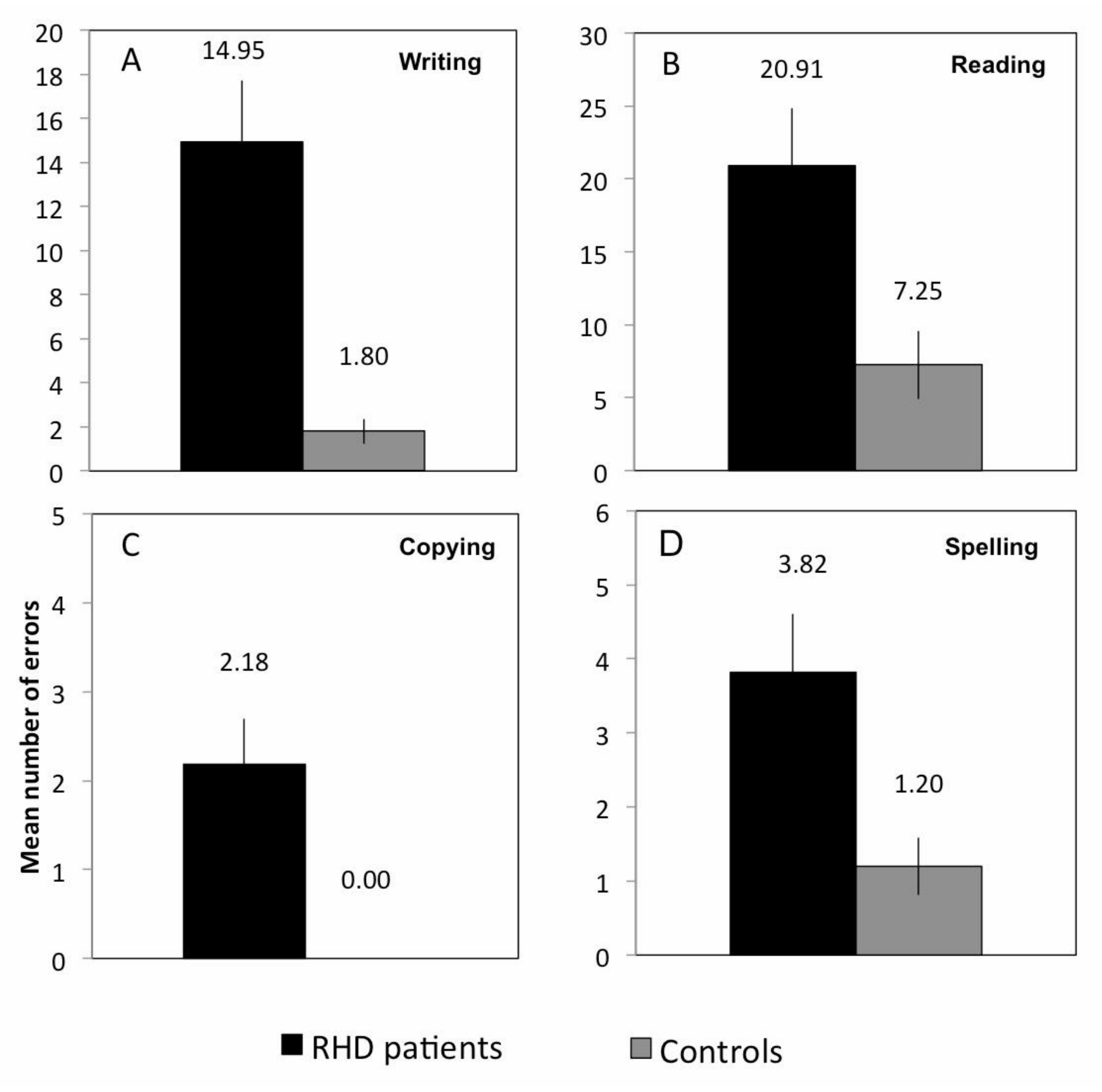
C.3.1. BEHAVIOURAL FINDINGS

In this section we quantitatively compare the absolute number of errors committed by patients and controls as a means to assess the magnitude of the hypothesized deficit of RHD patients in transcoding tasks. We also correlated the performance of the participants in the supplementary and transcoding tasks in order to investigate the implication of spatial, motor, and representational processes in transcoding. The group comparisons showed that patients performed significantly worse than the control group in all numerical processing tasks (writing Z = -3.86, $p < .0001$; reading Z = -2.43, $p < .01$; copying Z = -4.81, $p < .0001$; spelling Z = -2.97, $p < .001$) (see **Figure C.1**). Moreover, correlation analysis showed that the patients' performance in transcoding were associated with the spelling task [spelling and reading r =.69, $p < .001$; spelling and writing r =.73, $p < .001$], which relies on representational abilities. On the other hand, the copying task that relies mainly on visual or motor abilities did not correlate with any transcoding test. The same correlations were also significant when including all the participants in the analysis [spelling and reading r = .73, $p < .0001$; spelling and writing r = .74, $p < .0001$].

Additionally, we compared the error frequencies across items, as a means to evaluate our initial hypothesis that representing and processing numbers with *zeros* would be particularly difficult for right hemisphere-damaged patients. The ANOVA showed a main effect of item length (F(5, 390) = 25.78, $p < .0001$, $\eta\ p^2$ = 0.25) because of the significantly higher number of errors in the 5 and 6-digit items than in other items (5 vs 1,2,3 and 4 all four ps < .0001; 6 vs 1,2,3 and 4 all four ps < .0001). There was also a main effect of the number of *zeros* (F(4, 391) = 16.91, $p < .0001$, $\eta\ p^2$ = 0.15) because of significant differences between no-*zero* and one-*zero* items and 2,3, and 4-*zeros* items (no-*zero* vs 2,3 and 4-*zeros* all three ps < .0001; one-*zero* vs 2,3 and 4-*zeros* all three ps < .001). A similar analysis carried out in the group of healthy control participants also revealed a significant effect of item length (F(5, 354) = 4.3, $p < .001$). The number of *zeros* within a numeral, by contrast, did not have significant effects on the performance of the control group (F(4, 355) = .43, p = .78).

In a further analysis we explored the possibility that the patients' specific difficulties with *zeros* were only due to the increasing item-length associated with the increasing number of *zeros* in complex items. An analysis within digits of the same length ruled out this possibility. The results showed a main effect of number of *zeros* among 6-digit items (F(4, 105) = 2.70, $p < .05$, $\eta\ p^2$ = 0.10) because of a significant lower error rates in the no-*zero* items with respect to 2,3, and 4-*zero* items (all three ps < .005).

Figure C.1 | Performance of the participants on the four tasks.



A. Writing Arabic numerals to dictation. B. Reading Arabic numerals. C. Copying Arabic Numerals D. Spelling digits. Y-axis depict the mean number of errors per participant. Error bars indicate standard errors of the mean.

Finally, given that across items the *zeros* were frequently positioned next to each other, it is possible that the problems observed among patients could be related to stimulus similarity and attentional competition induced by similarity - rather than being specific to the number *zero*. To exclude this possibility we compared the number of patients erring items with repeated digits positioned next to each other (see Section C.2.4) with the number of patients making mistakes in items of the same length with repeated *zeros* located side by side. The results showed that the number of errors in the first group of items was significantly lower than in the *zero* items ($p < .01$). Moreover, an additional analysis comparing items with repeated digits (no-*zero*) positioned next to each other with a group of items of the same length containing one *zero* also showed significant differences due to a greater amount of errors in the items with *zero* ($p < .05$). This suggests that similarity alone cannot explain the results, rather the effects seems specific to the number *zero*.

C.3.2. Qualitative analysis of errors

A qualitative analysis of the errors allowed us to better characterize the numerical deficit in the RHD patients. **Table C.2** reports the type and frequency of errors made by the two groups in the transcoding and supplementary tasks. As expected, omission of digits in the left edge was among the most common errors of the patients in the copying task; its frequency was significantly higher than any other error (all *p*s < .01) and similar to the frequency of semantic errors not involving zeros. Patients also omitted digits while writing, and spelling; but significantly less so than the frequency with which they omitted internal *zeros* (both *p*s < .005). Insertion of *zeros* (irrespectively of whether it reflected the overwriting rule or not) was the most frequent error in writing (all *p*s < .005) and also among the most frequent mistakes in spelling (*p*s < .01; except for the category "omission of zeros" in which $p > .05$). For the reading task, instead, the most common mistake in patients was fragmentation. Noticeably, the frequency of fragmentation errors did not differ statistically from *zero* errors (i.e. overwriting, additions, omissions; all *p*s > .05) but it was significantly different from non-*zero* errors (additions $p < .001$; omissions $p < .05$). Fragmentation errors were also significantly more frequent than semantic errors either those involving ($p < .0001$) or not involving *zeros* ($p < .01$).

Table C.2 | Error types and frequencies across tasks.

	Reading				Writing				Copying				Spelling			
Type of error	**RHD**	**%**	**Controls**	**%**	**RHD**	**%**	**Controls**	**%**	**RHD**	**%**	**Controls**	**%**	**RHD**	**%**	**Controls**	**%**
Over-writing rule failure	55	11.78	4	2.78	130	37.14	2	5.71	-	-	-	-	18	21.43	0	0
Addition of *zeros*	45	9.64	4	2.78	111	31.71	7	20	3	6.25	0	0	30	35.71	12	50
Addition of digits (non *zero*)	2	0.43	0	0	3	0.86	0	0	0	0	0	0	2	2.38	0	0
Omissions of *zeros*	79	16.92	16	11.11	54	15.43	12	34.28	10	20.83	0	0	22	26.19	1	4.17
Omission of digits (non *zero*)	44	9.42	0	0	3	0.86	0	0	23	47.92	0	0	2	2.38	2	8.33
Semantic errors involving *zero*	3	0.64	0	0	22	6.29	2	5.71	0	0	0	0	6	7.14	3	12.5
Semantic errors not involving *zero*	29	6.21	4	2.78	27	7.71	12	34.28	12	25	0	0	4	4.76	6	25
Fragmentation	37	7.92	23	15.97	–	–	–	–	–	–	–	–	–	–	–	–
Fragmentation involving *zero*	165	35.33	93	64.58	–	–	–	–	–	–	–	–	–	–	–	–
Consecutive multiplicand	8	1.71	–	–	–	–	–	–	–	–	–	–	–	–	–	–

For each group of participants in each task, the absolute frequency of errors is presented in the first column. The second column indicates the relative frequency of the error type as compared to other error categories of the group in the same.

Controls' distribution of errors in all tasks differed considerably from that of the group of RHD patients (see **Table C.2**). Remarkably, failures in the overwriting rule were virtually absent in the healthy control group across tasks.

As a means to evaluate whether some of the categories of errors were associated with demographic variables, we performed regression analysis including age, MMS, and education as predictors. The results showed that the MMSE scores ($\beta = -1.06$; $p = .03$) and the level of education of the participants ($\beta = -.67$; $p = .01$) predicted the overall frequency of additions of *zeros* (Model $R^2 = .26$, $F(2,40) = 6.77$; $p = .003$). These two factors also predicted omissions of *zeros* [$\beta = -1.32$; $p = .0013$; $\beta = -.75$; $p = .0008$; Model $R^2 = .43$, $F(2, 40) = 14.68$; $p < .0001$] and lexical errors involving *zeros* [$\beta = -.20$; $p = .02$; $\beta = -.11$; $p = .01$; Model $R^2 = .28$, $F(2, 40) = 7.60$; $p = .002$]. MMSE alone predicted also the semantic errors not involving *zeros* ($\beta = -.51$; $p = .006$; Model $R^2 = .17$, $F(2, 40) = 8.58$; $p = .005$). These factors fail to predict the overwriting errors as well as other error categories.

C.3.3. Cognitive predictors of non-zero errors

Separate regression analyses were performed in order to identify some cognitive abilities at the basis of each category of errors. The patients' scores on the neuropsychological tests used for the regression analyses are reported in the Supplementary Material 8. Measures of *Neglect* (sections of BIT-C) predicted the number of additions ($\beta = -.01$; $p = .016$; Model $R^2 = .26$, $F(5, 15) = 6.96$; $p = .016$) and omissions of non-*zero* digits ($\beta = -.12$; $p = .001$; Model $R^2 = .41$, $F(8, 40) = 14.03$; $p = .001$). Moreover, fragmentation was predicted by measures of *Attention* ($\beta = -.12$; $p = 0.01$; Model $R^2 = .28$, $F(5,15) = 7.88$; $p = .001$). A further sub-division considering the position of the mistaken digit within the number (left-edge, right-edge, and internal positions) revealed that besides *Neglect*, measures of *Working memory* (i.e. digit span backward) predicted the patients' omissions of digits to the left edge ($\beta = -2.17$; $p = 0.003$; Model $R^2 = .73$, $F(5, 15) = 14.96$; $p = .0007$). Furthermore, *Executive Functions* (i.e. phonemic fluency) predicted additions of digits to the right edge (β =

−.02; $p = .009$; Model $R^2 = .44$, $F(5, 15) = 9.35$; $p = .009$). Other types of non-*zero* errors, including semantic ones, were not predicted by the neuropsychological tests.

C.3.4. Cognitive predictors of zero errors

The results of the regression analysis performed for each category of zero-errors showed that tests of *Representational Visuo-spatial abilities* predicted both addition ($\beta = -2.75$; $p < .001$; Model $R^2 = .47$, $F(5, 15) = 18.19$; $p < .001$) and omission of *zeros* ($\beta = -.35$; $p = .008$); the latter was also predicted by measures of *Short term memory* (i.e digit span forward) [$\beta = -3.63$; $p = .01$; Model $R^2 = .62$, $F(5, 14) = 14.90$; $p = .0001$). Results of other neuropsychological tests did not influence *zero*-errors.

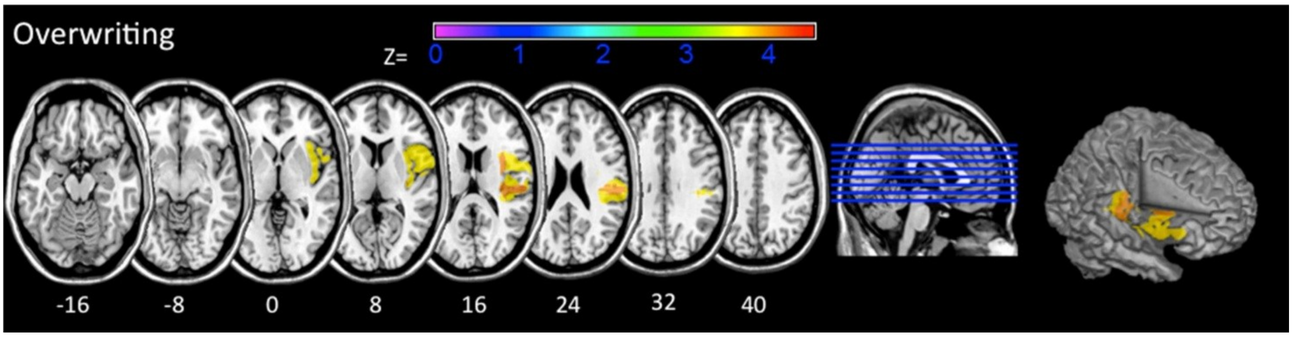
C.3.5. Brain areas significantly associated with specific error types

The goal of this analysis was to evaluate whether the frequency of each error category was associated to lesions in specific regions of the brain. To this aim we first performed an iterative cluster analysis (see **Table C.3**), which identified the group of patients showing a performance comparable to controls, and those patients whose performance was significantly lower than controls. The clusters were then used to feed the nonparametric Liebermeister test (see Section C.2.7). The findings indicated that patients showing abnormal amounts of overwriting errors had lesions maximally associated with the right insula (96% of its total volume felt within the significant z-map) and parts of the frontal inferior and Rolandic operculum, with lesions extended posteriorly towards the superior temporal gyrus (**Figure C.2**). The areas associated to other error types are shown in **Figure C.3**. Since the figure is not corrected for multiple comparisons, some caution must be exercised in interpreting these results. It was prominent, though, the association of right hemisphere areas with errors involving addition and omission of *zeros*.

Table C.3 | Distribution of patients according to the iterative cluster analysis.

Type of error	Patients with performance comparable to controls	Patients with abnormal performance
Over-writing rule failure	13	9
Addition of *zeros*	14	8
Addition of digits (no *zero*)	18	4
Omissions of *zeros*	13	9
Omission of digits (no *zero*)	15	7
Semantic errors involving *zero*	13	9
Semantic errors not involving *zero*	11	11
Fragmentation	14	8
Fragmentation involving *zero*	18	4
Consecutive multiplicand	21	1

Figure C.2 | VLSM for overwriting errors.

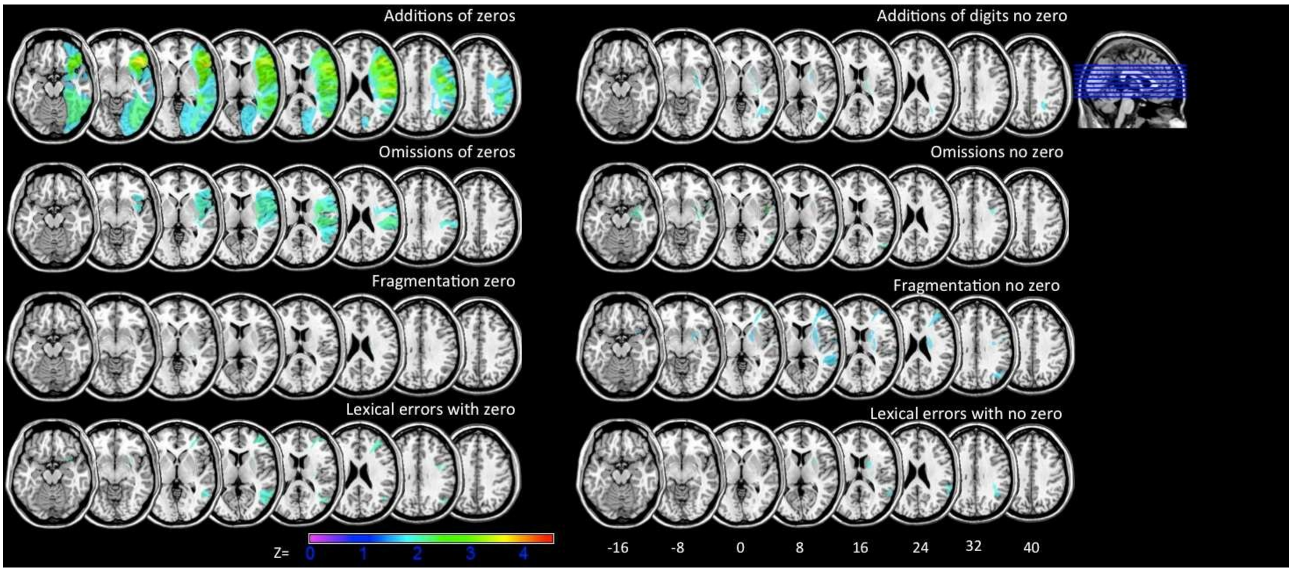


Statistical VLSM analysis comparing the patients who failed to implement the overwriting rule with patients who showed a performance comparable to controls. Presented are all voxels that were damaged significantly more frequently in the former and that survived a False Discovery Rate correction alpha level of P < 0.01. MNI coordinates of each transverse section are given.

C.4. Discussion

The goal of the present study was to identify brain areas and determine the cognitive processes associated to specific types of errors made by RHD patients when transcoding numbers. In particular, the study focused on transcoding *zeros* and the hypothetical role of the right cerebral hemisphere in dealing with this number.

Figure C.3 | VLSM for other error types.



Statistical VLSM analysis comparing the patients showing abnormal performance on the transcoding tasks with patients who showed a performance comparable to controls. Separate results are shown for each error type. Presented are all voxels that exceed an uncorrected P < 0.05. MNI coordinates of each transverse section are given.

C.4.1. The right hemisphere is required for transcoding complex digits containing zeros

The quantitative analysis of the behavioural data confirmed that significant transcoding deficits arise as a result of right hemisphere damage. These findings extend the pattern of results presented in previous studies on RHD patients, which reported difficulties in this group of patients but only moderate ones (Ardila & Rosselli, 1994; Basso et al., 2000; Rosselli & Ardila, 1989). Differences in the magnitude of the reported deficits are possibly due to the relatively low complexity of the stimuli used in previous studies. The present findings suggest, in fact, that the severity of the deficit in RHD patients emerges particularly while dealing with complex (long) numerals and worsen when the numerals contain several *zeros*. Unlike our own study, the studies of Ardila and Rosselli, and Basso *et al*. did not focus specifically on numbers containing *zeros*, thus giving rise to the lower error rates found in their cohort of RHD patients.

It has been hypothesized that the process of transcoding has cognitive costs resulting from the simultaneous maintenance of the input information (phonological or visuo-spatial) in working memory, the rules or procedures implementing transcoding that are retrieved from long-term memory, and the specific strings (numbers or words) resulting from these procedures (Barrouillet et al., 2004). This cognitive load is likely to increase with the size of the numbers to be transcribed (J. R. Anderson, 1993) and explains why patients –and controls– tend to have more difficulties with larger numbers. Dealing with complex numbers containing internal *zeros*, further increases the cognitive load. For example, in the writing to dictation task, transcoding a number such as *one hundred thousand and eighty-three* possibly requires procedures other than those required for transcoding a complex number of the same size which does not contain *zeros*. This is because the presence of internal *zeros* requires the subject not only to maintain in working memory the exact sequence of digits but also to determine the exact number of empty slots that should be filled with *zeros*. In fact, the position and the number of *zeros* are not explicitly suggested by the sequence of words, and consequently the string of digits resulting from the application of the transcoding rules. The online transcription of the empty-slot structure, namely writing down three *zeros* immediately after hearing *thousand* in the above example, may alleviate the cognitive load (Barrouillet et al., 2004), and possibly gives rise to overwriting errors such as *100 00083*. As it would be discussed below, carrying out complex transcoding tasks involving *zero* possibly requires highly specific processes whereby the right-hemisphere plays a crucial role.

The high frequency of *zero*-related errors in transcoding was indeed expected. In the Arabic number system *zero* is a particular case insofar as many rules apply exclusively to this digit. Unlike any other digit the null-value of *zero* does not change in relation to its position within a numeral. Furthermore, it is not always necessary to represent it in Arabic symbols (e.g. 8 instead of 08); and when functioning as a placeholder (e.g. 2014) it is not generally expressed in the verbal code of most languages (e.g. *duemila quattordici* (in English *two thousand and fourteen*) instead of *duemila* ***zero*** *quattordici* (in English *two thousand* ***zero*** *hundred fourteen*). Difficulties with *zero*, moreover, do not distinguish RHD patients only; they have been reported in a number of studies with children (Merritt & Brannon, 2013; Power & Dal Martello, 1990; Seron & Fayol, 1994; Zamarian, Granà, et al., 2007) and left hemisphere-damaged patients (Delazer & Denes, 1998; Deloche & Seron, 1982a, 1982b; Granà et al., 2003; Lochy, Domahs, Bartha, & Delazer, 2004; Semenza et al., 2006). What does seem to differentiate the right hemisphere-damaged patients from other groups is that their deficit (in absence of language problems) appears primarily when coping with *zeros*. In this study, the relative frequency of omissions, the addition and the semantic errors involving *zeros* reached about 40% of the reading and more than 90% of the writing errors in patients, compared to 17% and 65% in controls, respectively. Presence of numerical difficulties after right-hemisphere lesions is, therefore, not limited to omissions of left-sided digits, as previously suggested (see Priftis et al., 2013).

One possibility is that damage to the right hemisphere affects the construction and the use of empty-slot structures required for writing internal *zeros* in a dictation task; this explains the greater amount of overwriting errors and also the addition and omission of *zeros* in patients with this type of lesion. Right-hemisphere functions might be also implicated while applying the procedures to read a complex Arabic number such as 100003. Arguably, while carrying out this task, most people would strategically parse the number into groups of three digits (Deloche & Seron, 1987). In fact, the three-digit grouping respects both the way memory systems group items in span tasks (Hitch, 1996), and also the convention of writing complex Arabic digits in spatially separated chunks or categories (e.g. 100 003 or even 100.003). Then each chunk of a hierarchically-organised set can have a simple (Initial, Middle, End) structure. The use of this structure facilitates the processing of spatial relations and the positioning of digits in the number. Yet, in the absence of external cues or punctuation marks (e.g. commas in English, points in Italian) organisation of the categorical spatial relations between constituent digits resulting from the parsing process would be more difficult, given the computational difficulties of representing a larger serial ordering (Houghton, 1990). The present data show that this seems to be particularly so in right hemisphere-damaged patients who generally have difficulties in visuo-spatial tasks. As a consequence, these patients parse and read complex numbers in all sorts of ways (e.g. 100003 as *diecimila tre*, in English *ten thousand and three*; or *centomila zero zero tre*, in English *one hundred thousand zero zero three*). Furthermore, a failure to apply the parsing strategy combined with the patients' difficulties in mastering empty-slot structures results in the observed "omission of zeros" errors (e.g. *one thousand and three*).

It is thus possible that the greatest difficulties for people with right-hemisphere lesions in transcoding tasks are due to their impaired processing of internal zeros in complex numbers, which in turn depends on their problems in setting-up appropriate empty-slot structures, and in the parsing and mastering of categorical spatial relations between digits. This latter possibility fits well with the proposal that the implementation of categorical spatial relations is primarily a function of the right hemisphere, and depends particularly on the right parietal areas and parieto-frontal connections (Bricolo, Shallice, Priftis, & Meneghello, 2000; Buiatti, Mussoni, Toraldo, Skrap, & Shallice, 2011).

The specific deficit with zeros observed in RHD patients is in keeping with transcoding studies in Japanese (Furumoto, 2006) and justifies a more detailed investigation of the phenomenon. Thus, in what follows we summarize and discuss the major findings of the present work highlighting the differences observed between the *zero* and non-*zero* errors.

C.4.2. Neglect in RHD patients predicts non-zero errors

Spatial abilities are frequently related to the RHD patients' failures to carry out numerical tasks (Doricchi, Guariglia, Gasparini, & Tomaiuolo, 2005; Vuilleumier, Ortigue, & Brugger, 2004; Zorzi, Priftis, & Umiltà, 2002), but only in very few cases have they been the focus in neuropsychological studies of transcoding. Pioneer studies in the field adduced most transcoding errors to symptoms that are highly common among people who experienced right-hemisphere lesions, namely a processing failure of the left side of space (Dahmen et al., 1982; Rosselli & Ardila, 1989) and constructional apraxia (Basso et al., 2000). Unfortunately, the conclusions from those studies were mainly based on *post-hoc* observations and lacked statistical support. This called for a finer re-examination of the initial proposals.

In a recent study, our group assessed various numerical abilities, including writing and reading Arabic numerals, in 24 RHD patients (Benavides-Varela et al., 2014). The results showed a significant correlation between the patients' visuo-spatial faculties and their performance in transcoding tasks[5]. However, the restricted number of items of the battery – which was appropriately designed for clinical screening - did not allow further correlations with specific error categories. By providing a comprehensive qualitative and statistical analysis of errors, the present results contribute to further clarifying the relation between neglect and transcoding deficits RHD patients. The regression analysis confirmed the previous findings showing that neglect significantly predicts transcoding errors in right hemisphere-damaged patients. Moreover, the separate analysis of *zero* and non-*zero* errors provided a novel contribution by suggesting, for the first time, that this relationship applies only to non-*zero* errors. In fact, no Arabic number begins with left *zeros*. Thus, even though input-output errors in neglect patients arise irrespective of whether reading words, numbers, drawing, etc., they rarely implicate *zeros*.

We also noticed that the hypothesis anticipating a relationship between spatial abilities and numerical tasks mediated by constructional apraxia (Basso et al., 2000) seems incompatible with our findings. The correlational analysis between transcoding and supplementary tasks showed that both reading and writing errors in the present study significantly correlated with the spelling, not the copying task. This suggests that transcoding errors come about in the inner representations of spatial structures rather than the visual inputs or the motor outputs. This was confirmed by the results of the regression analysis showing that *Representational Visuo-spatial abilities* significantly predicted the type of errors which these patients produced most (*zero*-errors).

Finally, the data showed that the relative frequency of non-*zero* errors represent about 10% of the total reading errors and only 2.72% of the writing mistakes the patients made (see **Table C.2**). Therefore, the so-called "Neglect errors", namely omissions and addition of digits that are

[5] In line with other recent investigations of right-hemisphere acalculia (Furumoto, 2006; Granà et al., 2003), the study also revealed errors in other numerical tasks, which were not explained by the presence of neglect.

associated with the inability to process the left side of space and related visuo-spatial deficits, are modest and should not be considered the most crucial factor of the deficit.

C.4.3. Overwriting errors and their anatomical substrates

The failure to apply the overwriting rule was among the most conspicuous *zero*-related errors in this study, particularly in the writing task. It consists in systematically adding *zeros* in the middle of a complex numeral with the apparent rationale of reflecting the way the number is read in the linguistic code (i.e. *three thousand and sixty-five* → 300065).

The lesion analysis indicated that overwriting relies, among other regions, upon the right insular cortex and surrounding areas. The insula underpins a wide range of functions (e.g., Campanella, Shallice, Ius, Fabbro, & Skrap, 2014; Cona, Scarpazza, Sartori, Moscovitch, & Bisiacchi, 2015; Corradi-Dell'Acqua, Hofstetter, & Vuilleumier, 2011; Karnath & Baier, 2010; Karnath, Rorden, & Ticini, 2009; Menon & Uddin, 2010), yet its integrative role (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010; Singer, Critchley, & Preuschoff, 2009) appears particularly aligned with Power and Dal Martello's proposal describing "overwriting" as a merging operation (e.g. 3000#(60&5) → 3065).

It should be noted that a salient although not statistically robust involvement of right-hemisphere areas was also observed in other *zero*-errors (see **Figure C.3**). This pattern of activation further supports the participation of these brain areas in processing the internal representation of the *zero*. Remarkably, previous studies had also reported the involvement of the insula in numerical tasks. Yet here, for the first time, it is considered instrumental in the procedural sense of a number task and not merely due to experimental manipulations (Arsalidou & Taylor, 2011), working memory (Cowell, Egan, Code, Harasty, & Watson, 2000), or anxiety (Pesenti, Thioux, Seron, & De Volder, 2000).

We do not exclude the possibility that the critical lesions affecting the transcoding process are to the right superior longitudinal fasciculus connecting prefrontal regions with more posterior regions. This white matter tract has been linked to the subjects' performance on visuo-spatial tasks

(Shinoura et al., 2009; Vestergaard et al., 2011), and could be involved in mapping the numeral into a set of spatially organised slots. The results of the VLSM showed maps that border but do no overlap the superior longitudinal fasciculus. However, the conclusions from the current anatomical analysis are limited in this respect; if lesions affect different parts of the tract, then this will not necessarily show on the overlapping maps of a VLSM analysis.

Further comparisons with left-hemisphere damage patients could be highly informative as far as lateralization is concerned. However, such comparisons may be also problematic. From many previous studies one can predict a priori that an unselected sample of left-hemisphere damaged patients –comparable to our group of right-hemisphere damaged patients− will have language deficits that mask their number competence. One could attempt to eliminate this difference by selecting left-hemisphere damaged patients without language disorders, but this would make the sample less representative of the general hemisphere damage population and, more critically, it could have only a limited value because the areas supporting the processing of zero may well overlap with language areas.

Finally, the regression analysis of the present study also showed that one critical factor that predicts the frequency of unsystematic *zero*-errors (both in patients and controls) is the level of education and global cognitive functioning. This is not surprising, considering that the complex transformation rules required to cope with the positional base-10 system are almost entirely acquired through formal instruction. Our intuition is that previous neuropsychological studies investigating *zero*-errors in transcoding made no specific claims about the role of these variables since the majority reported single-case or small group studies.

C.5. CONCLUSION

The present study described transcoding error patterns emerging as a consequence of damage to the right-hemisphere, the cognitive functions, and some specific areas underlying those patterns. In particular, the data highlighted the role of the right-hemisphere for transcoding complex digits containing *zeros* and point to the right-insula and posterior portions of the superior temporal gyrus as possible areas implicated in transcoding internal *zeros*.

We conclude that right hemisphere-damaged patients struggle with *zeros* in complex numbers due to their difficulties in setting-up appropriate empty-slot structures, and in the parsing and mastering of the categorical spatial relations between digits. The integration of information resulting from the temporal application of transcoding rules (analogous to overwriting in Power and Dal Martello's model, 1990) is also impaired in these patients. Moreover, the patients' difficulties processing the left side of space lead to the so-called neglect errors, which however are less frequent and may not necessarily, depend on the processes required for dealing with *zeros*.

Zero appeared surprisingly late in history with respect to other numbers and complex mathematical concepts. The difficulties associated with its use are surely grounded in its many and unique mathematical functions. Distinguishing these functions from one another, by virtue of neuropsychological dissociations, constitutes a step forward in understanding how the brain actually processes *zero*. Here we show that some mechanisms underlying the operation of overwriting zeros -relying in turn on the capacity to merge the information derived from a previous intermediary process of transcoding-, can be singled out functionally and anatomically. Particularly we observe that processing *zeros* requires specific mechanisms mainly grounded in the right insula and possibly also right parieto-frontal connections. These mechanisms stand apart from other mechanisms necessary for completing such tasks, do not seem to be entirely reduplicated in the left hemisphere (otherwise right hemisphere-damaged patients would not present with the difficulties shown here), and do not entirely depend on generic processing resources.

SUPPLEMENTARY MATERIALS

Supplementary Material 1

The Supplementary Material for the **Study 1** can be found online at:

http://journal.frontiersin.org/article/10.3389/fnagi.2014.00112/full

Supplementary Material 2

Table S.2.1 | Composite measures of the neuropsychological tests.

Cognitive Domains	Neuropsychological Test
General Cognitive functioning	MMSE (Folstein et al., 1975)
Executive Function and Attention	Phonemic fluency (Novelli et al., 1986)
	Stroop (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002b)
	Digit Cancellation (Spinnler & Tognoni, 1987)
	Digit span backwards (Orsini, Grossi, Capitani, & Laiacona, 1987)
	Trial Making Test (A-B) (Giovagnoli et al., 1996)
Language	Semantic fluency (Novelli et al., 1986)
	Token test (Spinnler & Tognoni, 1987)
	Confrontation Naming
Short-term Memory	Digit span forward (Orsini et al., 1987)
	Immediate story recall (Spinnler & Tognoni, 1987)
	Spatial span (from Corsi block tapping) (Orsini et al., 1987)
	Rey Auditory Verbal Learning Test (immediate recall) (Carlesimo et al., 1996)
Long-term Memory	Delayed recall Rey Figure (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002a)
	Delayed story recall (Spinnler & Tognoni, 1987)
	Supraspan (from Corsi block tapping)
	Paired associate (Novelli et al., 1986)
	Rey Auditory Verbal Learning Test (delayed recall) (Carlesimo et al., 1996)
Visuo-spatial abilities	Immediate copy Rey Figure (Caffarra et al., 2002a)
Abstract reasoning	Raven Progressive Matrices (Carlesimo et al., 1996)
	Similarities (from Wechsler Adult Intelligence Scale - Revised)
Cognitive Reserve	Cognitive Reserve Index (Nucci et al., 2012)
Depression	Geriatric Depression Scale (short form) (Sheikh & Yesavage, 1986)
Everyday functional abilities	Instrumental abilities of Daily Living (Lawton & Brody, 1969)

Supplementary Material 3

Table S.3.1 | Demographic and clinical data of all the participants of Study 3.

Participant	MMSE	Gender	Age (years)	Education (years)
PZ_1	30	F	24	18
PZ_2	28	F	51	5
PZ_3	30	F	33	8
PZ_4	29	M	20	13
PZ_5	27	M	44	18
PZ_6	28	F	32	18
PZ_7	29	M	20	11
PZ_8	29	F	29	18
PZ_9	29	F	21	13
PZ_10	27	M	26	18
PZ_11	27	F	27	18
PZ_12	26	F	29	8
PZ_13	30	M	19	13
PZ_14	30	M	36	10
PZ_15	29	M	19	13
PZ_16	29	F	31	12
PZ_17	27	M	19	13
PZ_18	29	F	41	8
PZ_19	30	M	24	11
PZ_20	29	F	34	13
PZ_21	27	F	32	13
PZ_22	26	F	53	8
PZ_23	27	F	33	8
PZ_24	25	F	49	13
PZ_25	29	M	46	8
PZ_26	30	F	28	8
PZ_27	29	F	49	13
PZ_28	28	M	54	18

Participant	MMSE	Gender	Age (years)	Education (years)
NHP_1	28	M	32	13
NHP_2	30	M	26	18
NHP_3	29	M	40	13
NHP_4	30	M	45	16
NHP_5	30	F	27	18
NHP_6	30	M	51	8
NHP_7	29	F	51	8
NHP_8	30	F	37	13
NHP_9	27	M	37	13
NHP_10	30	M	29	16
NHP_11	30	F	49	13
NHP_12	30	M	25	18
NHP_13	30	M	46	13
NHP_14	29	F	27	18
NHP_15	28	F	36	13
NHP_16	30	M	26	18
NHP_17	26	F	51	8
NHP_18	29	F	51	8
NHP_19	28	M	36	18
NHP_20	25	F	48	8
NHP_21	27	F	43	8
NHP_22	30	M	39	11
NHP_23	30	F	33	13
NHP_24	30	M	38	10
NHP_25	30	M	21	13
NHP_26	29	F	50	8
NHP_27	29	F	24	13
NHP_28	26	M	40	13

Supplementary Material 4

Table S.4.1 | Summary of the demographic data of all the participants and the clinical data of the patients.

	Patients	Controls
Demographics		
Gender	M = 17; F = 13	M = 18; F = 17
Age (mean ± SD; range)	60 ± 13.3; 29−85	60 ± 12.2; 21−71
Education (mean ± SD; range)	11.1 ± 4.6; 5−23	10.9 ± 4.6; 5−20
Neuropsychological tests		
Neglect		
Mean ± SD; range	115.8 ± 36.6; 32−145	–
# patients below cut-off (124)	12	–
Total score = 139		
Executive Functions		
Mean ± SD; range	29.6 ± 10.9; 6−65	–
# patients below cut-off (17.7)	3	–
Short-term memory		
Mean ± SD; range	5.5 ± 1.1; 3−8	–
# patients below cut-off (4.26)	1	–
Total score = 8		
Working memory		
Mean ± SD; range	3.3 ± 1.1; 2−7	–
# patients below cut-off (2.65)	6	–
Total score = 8		
Attention		
Mean ± SD; range	33.7 ± 16.5; 16−59	–
# patients below cut-off (30)	9	–
Total score = 60		
Representational abilities		
Mean ± SD; range	3.6 ± 2.4; 0−7	–
# patients below cut-off (5)	22	–
Total score = 7		

Table S.4.2 | Types of errors in the patient's responses to the Formal assessment.

Task	Type of error	Description	Classification	Total number of errors (Relative frequency %)	Number of patients
Number Comprehension					
Number Comparison	Omissions in the left hemi-space	Failure to count or consider the squares in the left side of the display.	Spatial	9 (90%)	6
	Intrusions in the left hemi-space	Counting or considering more squares in the left side of the display than what they are.	Spatial	1 (10%)	1
Number Line	Leftward deviations	Failure to indicate the position of a number in a number line, deviating to the left of the reference.	Spatial	84 (49.7%)	25
	Rightward deviations	Failure to indicate the position of a number in a number line, deviating to the right of the reference.	Spatial	85 (50.3%)	25
Dot counting	Dot omissions	Failure to count or consider the dots in the left side of the display.	Spatial	42 (82.35%)	12
	Dot intrusions	Counting or considering more dots in the left side of the display than what they are.	Spatial	9 (17.65%)	6
Transcoding					
Reading	Lexical	Transcoding error leading to the production of a number of the same magnitude e.g., 24 → *twenty-six* (McCloskey et al., 1985).	Lexical	8 (44.44%)	8
	Syntactical	Transcoding error leading to the production of a number of different magnitude e.g., 24 → *two hundred and forty* (McCloskey et al., 1985).	Syntactical	11 (55.56%)	7
Writing	Lexical	Transcoding error leading to the production of a number of the same magnitude e.g., *twenty-four* → 26 (McCloskey et al., 1985).	Lexical	9 (56.25%)	9
	Syntactical	Transcoding error leading to the production of a number of different magnitude e.g., *twenty-four* → 240 (McCloskey et al., 1985).	Syntactical	7 (43.75%)	6

Mental Calculation					
Mental Addition	Digit errors	Omitting a digit or adding it twice as a result of not computing the sequence presented e.g., 2+3=8 (Brown, 1906 cit. in Spiers, 1987).	Numerical/ Arithmetical	1 (50%)	1
	Basic fact error	Computation involving an error in recalling basic number facts e.g., 5+7=13 (Engelhardt, 1977 cit. in Spiers, 1987).	Numerical/ Arithmetical	1 (50%)	1
Mental Subtraction	Subtraction Inversion	The minuend and subtrahend are reversed during the computation e.g. 13-4=1 (Spiers, 1987).	Numerical/ Arithmetical	3 (27.27%)	2
	Perseverative solution	Substitution of a number present in the problem into the number given as the solution e.g. 11-4=11; (Spiers, 1987).	Numerical/ Arithmetical	1 (9.09%)	1
	Basic fact error	Computation involving an error in recalling basic number facts e.g., 9-6=5 (Engelhardt, 1977 cit. in Spiers, 1987).	Numerical/ Arithmetical	6 (54.55%)	5
	No answer		—	1 (9.09 %)	1
Mental Multiplication	Operand error (far)	Product of an operand with another not included in the problem (McCloskey et al., 1991) and that is not the preceding/following operand in the times-table e.g., 8x9=36	Numerical/ Arithmetical	3 (10.71%)	3
	Operand error (close)	Product of an operand with another not included in the problem (McCloskey et al., 1991) but that corresponds to the preceding/following problem in the times-table e.g., 3x9=18; (called Approximation error in Della Puppa et al., 2013).	Numerical/ Arithmetical	9 (32.14%)	8
	Table error	The erroneous response is an answer to a single-digit problem that does not share an operand with the stimulus problem e.g., 9x6=64 (McCloskey et al., 1991).	Numerical/ Arithmetical	4 (14.29%)	3
	Non-table error	Solution not included in the times-table i.e., 8x9=62; (McCloskey et al., 1991; Sokol et al., 1991).	Numerical/ Arithmetical	5 (17.86%)	5
	No answer		—	7 (25.0%)	3

Rules and properties of Calculation					
Principles of calculation with Zero and One	Zero (rule) error	Basic fact errors occurring only when 0 is present in the problem e.g., 0x7=7; (McCloskey et al., 1991; Spiers, 1987).	Numerical/ Arithmetical	28 (93.3%)	16
	Basic fact error	Computation involving an error in recalling single digit basic number facts e.g., 3-3=3; (Engelhardt, 1977 cit. in Spiers, 1987).	Numerical/ Arithmetical	1 (3.33%)	1
	No answer		—	1 (3.33%)	1
Properties of Additions	Application of back up strategies (Siegler, 1988)	The calculation is performed instead of obtaining the result based on the premise and the properties of additions.	Numerical/ Arithmetical	5 (16.13%)	2
	Perseverative solution	Substitution of a number present in the problem into the number given as the solution (Spiers, 1987) or the solution of the previous problem. e.g. “if 60 + 29 = 89 then 61 + 29 = ?” answer: 89	Numerical/ Arithmetical	10 (32.26 %)	6
	Skipping tens	The solution has a larger or smaller tens units than required e.g., “if 68 + 43 = 111 then 111 – 43 = ?” answer: 78 instead of 68 (Brown, 1906 cit. in Spiers, 1987).	Numerical/ Arithmetical	2 (6.45%)	2
	Failure to apply the property	The patient understands the premise, and tries to apply the property but uses the wrong operand or operation e.g “if 60 + 29 = 89 then 61 + 29 =?” answer: 88	Numerical/ Arithmetical	4 (12.90%)	3
	Distortion	Distortion of digit shape or spatial orientation e.g., 61 → 41 (Hartje, 1987).	Spatial	1 (3.23%)	1
	Omission of the leftmost digit	Failure to consider the digits on the left side of a number leading to wrong answers e.g., 370+180=150 (Hartje, 1987).	Spatial	1 (3.23%)	1
	Omission of the rightmost digit	Failure to consider the digits on the right side of a number leading to wrong answers e.g., 370+180=515 (Hartje, 1987).	Spatial	1 (3.23%)	1

	Syntactical	While the patient said the correct solution, he wrote a number of different magnitude e.g. *five hundred and five* → 5050 (McCloskey et al., 1985).	Syntactical	1 (3.23%)	1
	Random responses	There is no discernible relationship with the given problem e.g. "if 68 + 43 = 111 then 111 – 43 = ?" answer: 468 (Roberts, 1968 cit. in Spiers, 1987).	—	1 (3.23%)	1
	No answer		—	5 (16.13%)	4
Properties of Multiplication	Defective algorithm	The patient uses incorrect, inconsistent or idiosyncratic procedure e.g. 64+64+64+64+64=four multiplied by five is twenty, six and four is sixty-four, and sixty-four is hundred and twenty-eight (Spiers, 1987).	Numerical/ Arithmetical	4 (12.90%)	4
	Application of back up strategies (Siegler, 1988)	The calculation is performed instead of obtaining the result based on the premise and the properties of multiplication.	Numerical/ Arithmetical	8 (25.80%)	5
	Basic fact error	Computation involving an error in recalling single digit number facts e.g., If 94 x 5 = 470 then 93 x 5=?, answer= it should be 470 minus 5, thus= 466 (Engelhardt, 1977 cit. in Spiers, 1987).	Numerical/ Arithmetical	1 (3.23%)	1
	Perseverative solution	Substitution of a number present in the problem into the number given as the solution (Spiers, 1987) or the solution of the previous problem. e.g. "if 94 x5 =470 then 93x5=?" answer= 470	Numerical/ Arithmetical	11 (35.48%)	9
	Random responses	No discernible relationship with the given problem e.g. "if 34 x 6 = 204 then 204 / 6 = ?" answer: 46 (Roberts, 1968 cit. in Spiers, 1987).	—	2 (6.45%)	1
	No answer		—	5 (16.13%)	2
Multi-digit written operations					
Written Addition	Basic fact error	Computation involving an error in recalling single digit number facts e.g., 749+120=919 (Engelhardt, 1977 cit in Spiers, 1987).	Numerical/ Arithmetical	16 (36.36%)	9

	Neglect of "carry"	Failure to use a verbalized or clearly indicated "carry" in the process of computation e.g. 58+43=91 (Spiers, 1987).	Numerical/ Arithmetical	7 (15.91%)	6
	Omission of the leftmost digit	Failure to consider the digits on the left side of a number leading to wrong answers e.g., 463+659=122 (Hartje, 1987).	Spatial	3 (6.82%)	3
	Operation	A response that is correct for a problem involving the same operands as the stimulus problem, but a different arithmetic operation e.g., 749+120=629 (McCloskey et al., 1991).	Numerical/ Arithmetical	1 (2.27%)	1
	Distortion	Distortion of digit shape or spatial orientation e.g., 825 → 325 (Hartje, 1987).	Spatial	1 (2.27%)	1
	Zero (rule) error	Basic fact errors occurring only when 0 is present in the problem e.g., 749+120=860 (McCloskey et al., 1991; Spiers, 1987).	Numerical/ Arithmetical	2 (4.55%)	2
	Skipping columns	During the calculation one column, not necessarily the leftmost, is skipped (Hartje, 1987).	Spatial	1 (2.27%)	1
	Local errors in the process of "carrying"	The digits that must be "carried" are misplaced, leading to wrong solution of the problem e.g., 463+659=1211 (Hartje, 1987).	Spatial	6 (13.64%)	4
	Random responses	There is no discernible relationship with the given problem e.g. 370+180= 351 (Roberts, 1968 cit. in Spiers, 1987).	—	7 (15.91%)	6
Written Subtraction	Borrow failure	The higher place-holding digit is not reduced after a clearly verbalized or indicated borrow e.g. 62-18=54 instead of 44 (Spiers, 1987).	Numerical/ Arithmetical	14 (20.90%)	10
	Basic fact error	Computation involving an error in recalling single digit number facts e.g., 749+120=919 (Engelhardt, 1977 cit. in Spiers, 1987).	Numerical/ Arithmetical	17 (25.37%)	9
	Subtraction Inversion	The minuend and subtrahend are reversed during the computation e.g. 62-18=56 instead of 44 (Spiers, 1987).	Numerical/ Arithmetical	17 (25.37%)	13

	Omission of the leftmost digit	Failure to consider the digits on the left side of a number leading to wrong answers e.g. 548-231 → 48-231=217 (Hartje, 1987).	Spatial	2 (2.99%)	2
	Partial reversal	A set of digits in a number is written, copied or repeated in reverse e.g. 456-132 → 546-132 (Spiers, 1987).	Spatial	2 (2.99%)	2
	Distortion	Distortion of digit shape or spatial orientation e.g., 324 → 424; (Hartje, 1987).	Spatial	1 (1.49%)	1
	Operation	A response that is correct for a problem involving the same operands as the stimulus problem, but a different arithmetic operation e.g., 546-132=474 (McCloskey et al., 1991).	Numerical/ Arithmetical	4 (5.97%)	3
	Inversion of terms	The factors are inverted when placing them in columns e.g. 548-231 → 231-548	Spatial	2 (2.99%)	2
	Random responses	There is no discernible relationship with the given problem e.g 632-278=3449 (Roberts, 1968 cit. in Spiers, 1987).	—	6 (8.96%)	5
	No answer		—	2 (2.99%)	1
Written Multiplication	Misalignment	Irregular vertical alignment of digits or numbers in columns (Hartje, 1987).	Spatial	9 (10.11%)	7
	Local errors in the process of "carrying"	The digits that must be "carried" are misplaced, leading to wrong solution of the problem (Hartje, 1987).	Spatial	1 (1.12%)	1
	Basic fact error	Computation involving an error in recalling single-digit number facts (Engelhardt, 1977 cit. in Spiers, 1987).	Numerical/ Arithmetical	4 (4.49%)	4
	Skipping column	During the calculation one column, not necessarily the leftmost, is skipped e.g. 429x53=2737 (Hartje, 1987).	Spatial	1 (1.12%)	1
	Table error	The erroneous response is an answer to a single-digit problem that does not share an operand with the stimulus problem (Girelli et al., 1996; McCloskey et al., 1991).	Numerical/ Arithmetical	1 (1.12%)	1

Operand error (far)	Product of an operand with another not included in the problem (McCloskey et al., 1991) and that is not the preceding/following operand in the times-table e.g., 25x8=36	Numerical/ Arithmetical	1 (1.12%)	1
Operand error (close)	Product of an operand with another not included in the problem (McCloskey et al., 1991) but that corresponds to the preceding/following problem in the times-table e.g., 4x5=25; (called Approximation error in Della Puppa et al., 2013).	Numerical/ Arithmetical	7 (7.87%)	4
Distortion	Distortion of digit shape or spatial orientation (Hartje, 1987).	Spatial	2 (2.25%)	2
Omission of the leftmost digit	Failure to consider the digits on the left side of a number leading to wrong answers (Hartje, 1987).	Spatial	6 (6.74%)	5
Operation	A response that is correct for a problem involving the same operands as the stimulus problem, but a different arithmetic operation (McCloskey et al., 1991).	Numerical/ Arithmetical	3 (3.37%)	2
Omission	Failure to use a number or digit present in the problem during the computation (Spiers, 1987).	Spatial	5 (5.62%)	3
Zero (rule) error	Basic fact errors occurring only when 0 is present in the problem e.g., 618x0=618 (McCloskey et al., 1991; Spiers, 1987).	Numerical/ Arithmetical	8 (8.99%)	3
Defective algorithm	The patient uses incorrect, inconsistent or idiosyncratic procedure e.g. 25x8=4016 (Spiers, 1987).	Numerical/ Arithmetical	5 (5.62%)	4
Incomplete algorithm	Patient initiates the correct operation but fails to carry out all of the steps required to arrive at a solution and leaves the problem or some intermediate step incomplete e.g., 34x16=204 (Spiers, 1987).	Numerical/ Arithmetical	6 (6.74%)	5
Failure to carry	Failure to use a verbalized or clearly indicated “carry” in the process of computation (Spiers, 1987).	Numerical/ Arithmetical	5 (5.62%)	4

Random responses	There is no discernible relationship with the given problem e.g 429x53=125 (Roberts, 1968 cit. in Spiers, 1987).	—	16 (17.98%)	8
No answer		—	9 (10.11%)	4

Error types identified among the patients' responses in the Formal assessment, their description and classification. The table also shows the absolute and relative frequency of errors by task, and the number of patients committing each type of error.

Table S.4.3 | Error types divided by task and corresponding measures predicting the errors in RHD patients.

Task	Type of error	Cognitive Predictors	Regression coefficient	Model
Number Comprehension				
Dot Counting/Comparison	Omissions and intrusions	Attention/Neglect	β = −2.47; $p < .0001$	$R^2 = .64$; $F(2, 26) = 50.93$; $p < .0001$
Number Line	Deviations	Attention/Neglect	β = −1.67; $p < .0001$	$R^2 = .41$; $F(2, 26) = 19.70$; $p < .0001$
Transcoding				
Reading	Lexical	—	—	—
	Syntactic	Attention/Neglect	β = −.36; $p < .005$	$R^2 = .29$; $F(2, 26) = 11.39$; $p < .005$
Writing	Lexical	—	—	—
	Syntactic	—	—	—
Mental Calculation				
Mental Addition	Numerical/arithmetical	—	—	—
	Spatial	—	—	—
Mental Subtraction	Numerical/arithmetical	—	—	—
	Spatial	—	—	—
Mental Multiplication	Numerical/arithmetical	Representational abilities	β = −.20; $p < .05$	$R^2 = .17$; $F(2, 26) = 5.37$; $p < .05$
	Spatial	—	—	—

Rules and Properties				
Principles of operations with zero and one	Numerical/arithmetical	—	—	—
	Spatial	—	—	—
Properties of Addition	Numerical/arithmetical	—	—	—
	Spatial	Attention/Neglect	β = −.24; $p < .05$	$R^2 = .21$; $F(2, 26) = 7.53$; $p < .05$
Properties of Multiplication	Numerical/arithmetical	Representational abilities	β = −.38; $p < .05$	$R^2 = .18$, $F(2, 26) = 6.36$; $p < .05$
	Spatial	—	—	—
Written Calculation				
Additions	Numerical/arithmetical	Representational abilities	β = −.50; $p < .05$	$R^2 = .18$; $F(2, 26) = 6.23$; $p < .05$
	Spatial	—	—	—
Subtractions	Numerical/arithmetical	Representational abilities	β = −.91; $p < .005$	$R^2 = .27$; $F(2, 26) = 10.36$; $p < .005$
	Spatial	—	—	—
Multiplications	Numerical/arithmetical	—	—	—
	Spatial	—	—	—

Supplementary Material 5

A) Interview for Parents

The interview for parents included the following questions:

General information

1. Name of the child
2. Age in years and months
3. Number of brothers/sisters and their respective age
4. Occupation of the father
5. Occupation of the mother
6. Last degree/level of education obtained by the father
7. Last degree/level of education obtained by the mother

Health

8. Did the child or the mother had problems during the pregnancy? If yes, which ones?
9. Was the child born at term? If not, please indicate the number of weeks of the pregnancy.
10. Does the child have any important health problem? Was he/she healthy during the firsts years of life?
11. Does the child have any hearing problem diagnosed?
12. Does the child have any visual problem diagnosed? If yes, please specify if he/she uses glasses to correct the problem.

Daily activities

13. Which one of these activities do you and your child do together? (please specify how many times and hours per week)

    a- Shopping

b- Watching TV

c- Reading

d- Practice sports (How many? which ones? Do they require scoring? Is the child able to keep the scores by him/herself?)

e- Play board games (How many? which ones?)

f- Play videogames (How many? which ones?)

g- Other (please specify)

14. How many hours and how many times per week does your child spend in the following activities (do not consider the time he/she spends with adults in this activities):

a- Watching TV

b- Reading

c- Practice sports (which ones? How many?)

d- Play videogames (How many? which ones?)

e- Play outside with other children

f- Play an instrument (How many? which ones?)

g- e- Play alone with toys

h- Other (please specify)

Knowledge of number related information

15. Which one of these activities is your child able to do without help? (only questions marked with asterisk were including in the scoring. Additional questions were used as fillers)

a- (*) Count until 10

b- (*) Count until 30

c- (*) Tell his/her age

d- (*) Tell his/her birthday by heart

e- (*) Tell his/her address

f- Measure his/her own height

g- Measure his/her own weight

h- (*) Dial a phone number

i- (*) Tell the current time

j- (*) Tell the current date/year

k- (*) Tell the number of brothers/sisters and their age

l- Indicate whether he/she is late for school or any other activity

m- Get the money necessary to pay by him/herself for instance a bus ticket/train ticket

n- Choose the correct bus/train

o- Take the initiative to save money

p- Organize his/her own money to be able to buy stickers/ice-cream etc.

q- Cross the street

r- Ride a bike

B) Questionnaire for Children

Only questions marked with asterisk were including in the scoring.

Additional questions were used as fillers.

Hi_________ (name of the child) ____________!

1. (*) Could you tell me how old are you?
2. (*) When is your birthday?
3. (*) Do you remember in which year you were born?
4. (*) Do you have brothers and sisters? How many? How old are they?
5. (*) Could you tell me the address of your house?
6. Do you know what day of the week is today?
7. (*) What is the year?
8. (*) Do you know what date is today?
9. (*) Can you tell me the time? (if the child does not have a watch show him/her one so that he/she can answer).
10. (*) Could you give me the phone number of your mother or father?
11. What is your favourite game?
12. (*) Ok, now could you please show me how you count? (stop the child at 30).
13. How many children are there in the class?

Supplementary Material 6

Descriptive Statistics for NADL-F task scores

The following tables report the means, standard deviations, median, minimum, maximum, kurtosis, skewness, first quartile, and third quartile for NADL-F tasks scores in the normative data group of 120 healthy participants, divided in four groups according to different age and education combinations.

Table S.6.1 | Descriptive statistics

	Mean	SD	Median	min	max	Kurtosis	Skewness	Q1	Q3
Age < 70 years , Education ≤ 13 years									
Counting Currencies	4.78	0.54	5	3	5	4.01	−2.25	5	5
Reading Abilities	6.53	0.81	7	4	7	2.74	−1.81	6	7
Purchase	13	1.35	14	10	14	−0.28	−1.08	12.75	14
Percentages	7.14	2.04	8	2	9	−0.22	−0.98	6	9
Financial Concepts	8.53	2.29	8	5	13	−1.12	0.52	7	11
Bills	4.86	1.02	5	3	6	−1.11	−0.36	4	6
Financial Judgements	5.56	0.73	6	3	6	2.36	−1.66	5	6
Age < 70 years , Education > 13 years									
Counting Currencies	4.95	0.21	5	4	5	15.27	−4.07	5	5
Reading Abilities	6.77	0.43	7	6	7	−0.55	−1.21	7	7
Purchase	13.41	1.05	14	10	14	3.29	−1.99	13	14
Percentages	7.64	1.26	8	5	9	−1.13	−0.43	7	9
Financial Concepts	10.32	2.21	10	6	14	−0.8	0.12	9	11.75
Bills	5.14	1.04	5	2	6	1.28	−1.23	5	6
Financial Judgements	5.68	0.57	6	4	6	1.04	−1.45	5.25	6

Table S.6.2 | Descriptive statistics *(continue)*.

	Mean	SD	Median	min	max	Kurtosis	Skewness	Q1	Q3
Age ≥ 70 years , Education ≤ 13 years									
Counting Currencies	4.51	1.05	5	1	5	3.79	−2.17	5	5
Reading Abilities	5.81	1.28	6	2	7	1.7	−1.4	5	7
Purchase	11.63	2.59	12	3	14	2.15	−1.6	11	13
Percentages	5.28	2.53	5	0	9	−1.06	−0.26	3.5	7
Financial Concepts	8.12	2.64	8	3	13	−0.75	0.12	6	10
Bills	4.42	1.42	5	1	6	−0.71	−0.65	3.5	5.5
Financial Judgements	5.21	1.26	6	2	6	0.55	−1.35	4.5	6
Age ≥ 70 years , Education > 13 years									
Counting Currencies	4.89	0.32	5	4	5	3.84	−2.37	5	5
Reading Abilities	6.74	0.45	7	6	7	−1.06	−0.99	6.5	7
Purchase	12.68	1.92	13	7	14	1.62	−1.55	12.5	14
Percentages	7.47	1.47	8	4	9	−0.44	−0.7	7	9
Financial Concepts	9.42	2.04	10	6	12	−1.41	−0.28	8	11
Bills	5.32	0.67	5	4	6	−0.97	−0.4	5	6
Financial Judgements	5.78	0.55	6	4	6	3.61	−2.16	6	6

Cut-offs

The following tables report cut-offs for all NADL-F tasks scores. The cut-offs were calculated with the method by Crawford and Garthwaite (2006), using regression analyses taking into account age, education and gender. The tables report the cut-offs for different age and education combinations. Tables are split according to gender for those tasks in which gender was a significant variable. An observed value below the cut-off indicates an impaired performance. In particular, it is estimated that less than 5% of the population will obtain a score below the cut-offs reported in the tables. Notice that in some cases no effect of age or education is appreciable in the cut-offs table, even if significant in the regression analyses reported in the manuscript. This is a consequence of small but significant age or education effects, and of the approximation of cut-offs to the nearest integer.

Table S.6.3 | NADL–F Cut-Offs.

Education	Age							
	50	**55**	**60**	**65**	**70**	**75**	**80**	**85**
Counting Currencies								
5	3	3	3	3	3	3	3	3
8	3	3	3	3	3	3	3	3
13	3	3	3	3	3	3	3	3
18	3	3	3	3	3	3	3	3
22	3	3	3	3	3	3	3	3
Reading Abilities								
5	4	4	4	4	4	4	4	4
8	5	5	5	5	5	5	5	5
13	6	6	6	6	6	6	6	6
18	6	6	6	6	6	6	6	6
22	6	6	6	6	6	6	6	6
Item Purchase								
5	9	9	8	8	8	8	8	7
8	10	10	10	10	10	9	9	9
13	11	11	11	10	10	10	10	9
18	11	11	10	10	10	10	10	9
22	12	12	12	11	11	11	11	11

Table S.6.4 | NADL–F Cut-Offs *(continue)*.

Education	Age							
	50	55	60	65	70	75	80	85
Percentages (gender = female)								
5	1	1	1	1	1	1	1	1
8	2	2	2	2	2	2	2	2
13	4	4	4	4	4	4	4	4
18	5	5	5	5	5	5	5	5
22	5	5	5	5	5	5	5	5
Percentages (gender = male)								
5	2	2	2	2	2	2	2	2
8	3	3	3	3	3	3	3	3
13	5	5	5	5	5	5	5	5
18	5	5	5	5	5	5	5	5
22	6	6	6	6	6	6	6	6
Financial Concepts								
5	3	3	3	3	3	3	3	3
8	4	4	4	4	4	4	4	4
13	5	5	5	5	5	5	5	5
18	6	6	6	6	6	6	6	6
22	7	7	7	7	7	7	7	7
Bills Payments								
5	2	2	2	2	2	2	2	2
8	3	3	3	3	3	3	3	3
13	4	4	4	4	4	4	4	4
18	4	4	4	4	4	4	4	4
22	3	3	3	3	3	3	3	3
Financial Judgments								
5	4	4	4	4	4	4	4	4
8	4	4	4	4	4	4	4	4
13	4	4	4	4	4	4	4	4
18	4	4	4	4	4	4	4	4
22	4	4	4	4	4	4	4	4

Supplementary Material 7

Table S.7.1 | Composite measures of the neuropsychological tests.

Cognitive Domains	Neuropsychological Test
General Cognitive functioning	MMSE (Folstein et al., 1975)
Executive Function and Attention	Phonemic fluency (Novelli et al., 1986)
	Stroop (Caffarra et al., 2002b)
	Digit Cancellation (Spinnler & Tognoni, 1987)
	Digit span backwards (Orsini et al., 1987)
	Trial Making Test (A-B) (Giovagnoli et al., 1996)
Language	Semantic fluency (Novelli et al., 1986)
	Token test (Spinnler & Tognoni, 1987)
	Confrontation Naming
Short-term Memory	Digit span forward (Orsini et al., 1987)
	Immediate story recall (Spinnler & Tognoni, 1987)
	Spatial span (from Corsi block tapping) (Orsini et al., 1987)
	Rey Auditory Verbal Learning Test (immediate recall) (Carlesimo et al., 1996)
Long-term Memory	Delayed recall Rey Figure (Caffarra et al., 2002a)
	Delayed story recall (Spinnler & Tognoni, 1987)
	Supraspan (from Corsi block tapping)
	Paired associate (Novelli et al., 1986)
	Rey Auditory Verbal Learning Test (delayed recall) (Carlesimo et al., 1996)
Visuo-spatial abilities	Immediate copy Rey Figure (Caffarra et al., 2002a)
Abstract reasoning	Raven Progressive Matrices (Carlesimo et al., 1996)
	Similarities (from Wechsler Adult Intelligence Scale - Revised)
Cognitive Reserve	Cognitive Reserve Index (Nucci et al., 2012)
Depression	Geriatric Depression Scale (short form) (Sheikh & Yesavage, 1986)
Everyday functional abilities	Instrumental abilities of Daily Living (Lawton & Brody, 1969)

Supplementary Material 8

Table S.8.1 | Demographic and clinical data of all the participants (Appendix C).

Participant	MMSE	Gender	Age (years)	Education (years)	Lesion type
PZ_1	28	M	69	5	HS
PZ_2	25	M	61	8	IS
PZ_3	28	F	38	8	IS
PZ_4	29	M	50	13	IS
PZ_5	29	F	45	8	IS
PZ_6	27	M	59	13	IS
PZ_7	29	M	62	13	IS
PZ_8	28	M	71	13	IS
PZ_9	21	M	70	8	HS
PZ_10	27	M	75	18	IS
PZ_11	27	F	56	13	HS
PZ_12	27	M	61	8	IS
PZ_13	24	F	41	8	LTR
PZ_14	29	M	63	5	HS
PZ_15	29	M	67	13	HS
PZ_16	27	M	64	17	HS
PZ_17	29	M	57	13	IS
PZ_18	28	F	63	15	HS
PZ_19	21	F	77	12	IS
PZ_20	26	F	72	12	LTR
PZ_21	28	M	29	16	HS
PZ_22	30	F	48	17	IS
NHP_1	29	F	57	6	—
NHP_2	29	M	57	8	—
NHP_3	30	F	64	13	—
NHP_4	30	F	68	13	—
NHP_5	30	F	39	11	—
NHP_6	30	M	65	10	—
NHP_7	30	M	78	13	—
NHP_8	30	M	59	8	—
NHP_9	30	F	64	5	—
NHP_10	29	F	54	17	—
NHP_11	28	M	56	8	—
NHP_12	29	M	58	15	—
NHP_13	28	F	76	8	—
NHP_14	28	M	74	10	—
NHP_15	26	M	72	12	—
NHP_16	29	F	60	14	—
NHP_17	29	F	61	13	—
NHP_18	29	M	66	10	—
NHP_19	30	F	68	17	—
NHP_20	29	M	65	22	—

IS = ischemic stroke; HS = haemorrhagic stroke; LTR = Lesion caused by brain tumour removal
PZ = Right-hemisphere damaged patient; NHP = Neurologically healthy participant

Table S.8.2 | List of stimuli used in the transcoding tasks.

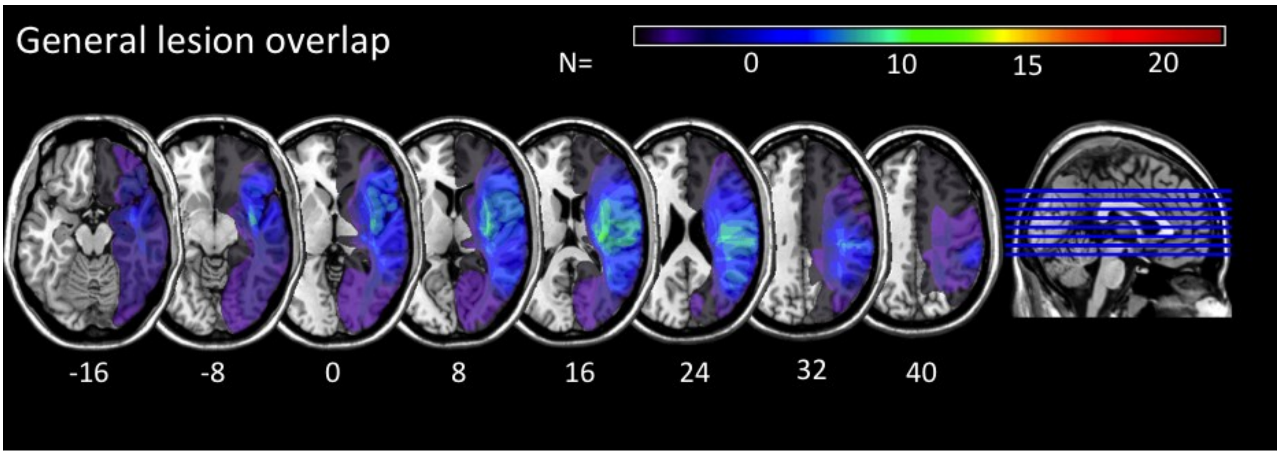
Item length	Number of zeros	Items
Reading task		
1 digit	—	1,5,8,9
2 digit	—	13,16,29,61
2 digit	1	20,50,80,90
3 digit	—	564,692,836,971
3 digit	1	310,430,708,801
3 digit	2	100,200,600,800
4 digit	—	1333,1367,2929,4114,6732,7623,8495,8843
4 digit	1	1089,2530,3404,3650,5630,7089,8230,9204
4 digit	2	1003,2003,2020,3030,4002,7002,7200,9900
5 digit	—	16947,25726,41673,43766,45322,61211,68539,69638
5 digit	1	10482,21850,34034,57605,57802,71230,74083,90321
5 digit	2	24006,34003,58060,61700,70013,90038,98001,98060
5 digit	3	30040,50030,50080,60070,70002,70006,80001,90005
6 digit	—	123436,164528,376254,483761,543876,683612,787234,789634
6 digit	1	107538,310756,531074,604938,730816,753102,825074,916702
6 digit	2	150058,170068,269009,362009,450073,543006,850013,962006
6 digit	3	208005,300607,370001,400098,601005,780001,800107,900058
6 digit	4	101000,200060,209000,300200,400040,500006,600006,800700
Writing to dictation task		
1 digit	—	4,5,7,8
2 digit	—	13,15,49,76
2 digit	1	10,30,60,80
3 digit	—	269,465,683,781
3 digit	1	108,230,506,910
3 digit	2	200,500,700,900
4 digit	—	6312,6543,6843,9267
4 digit	1	2304,5430,6089,6100
4 digit	2	1010,6002,8003,9500
5 digit	—	18234,36287,46879,76237
5 digit	1	14034,47802,60482,91230
5 digit	2	28010,30017,36002,65070
5 digit	3	10050,20003,60040,90006
6 digit	—	164528,683612,789634,978145
6 digit	1	107539,310757,531075,753103
6 digit	2	150059,269010,850014,962007
6 digit	3	300608,370002,400099,908004
6 digit	4	100003,100080,100700,102000

Table S.8.3 | Patients' performance on neuropsychological tests.

Patient	BIT-C	Phonemic Fluency[A]	Phonemic Fluency[B]	Digit span forward	Digit span backwards	Digit Cancellation[A]	Digit Cancellation[B]
PZ_1	111	28	3	6	2	21	0
PZ_2	104	29	3	5	4	20.75	0
PZ_3	115	31	3	6	4	48.75	3
PZ_4	137	6	0	4	3	45.5	3
PZ_5	112	24	2	5	4	27.5	0
PZ_6	126	27	3	6	2	16	0
PZ_7	144	42	4	5	3	59	4
PZ_8	47	20	1	6	2	16.5	0
PZ_9	144	21	1	6	3	51.5	4
PZ_10	143	42	4	6	3	32.25	1
PZ_11	120	21	1	5	3	37	2
PZ_12	129	30	3	6	2	50.75	4
PZ_13	124	29	3	4	3	43.75	2
PZ_14	139	36	4	5	5	40.5	2
PZ_15	135	15	0	6	4	42.75	2
PZ_16	136	28	1	7	5	42.25	2
PZ_17	142	39	4	5	5	48	3
PZ_18	140	57	4	5	5	45.1	3
PZ_19	98	26	2	5	2	23	0
PZ_20	140	65	4	6	3	46.25	3
PZ_21	145	28	3	7	4	35.25	1
PZ_22	134	36	4	7	7	34.75	1

[A] *Corrected score*
[B] *Equivalent score*

Figure S.8.1 | Lesion overlap across all patients.



MNI coordinates of each transverse section are given.