Arithmetic and the brain: a direct cortical electrostimulation study on two patients with intractable epilepsy.

Josje Kal

3160025

Masterthesis Neuropsychology

Utrecht University & University Medical Centre Utrecht

Supervisors: dr. H.C. Dijkerman & dr. M.J.E. van Zandvoort

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Abstract

In the last decades, much research has been done on the neural basis of number processing and arithmetic. Most studies have used fMRI, a technique that does not differentiate between brain areas which are essential for calculation and areas which are only involved. A technique that does not possess this disadvantage is direct cortical electrostimulation. In the current study direct cortical electrostimulation has been used to investigate the neural basis of arithmetic by testing two patients with intractable epilepsy, who had been selected for brain surgery. Clarifying the neural substrate of calculation contributes to the preserving of arithmetic abilities during neurosurgical interventions in these patients. The preoperative and postoperative results of the patients have been compared and the performances of the patients have been compared to those of a healthy control group as well. A new digital arithmetic task has been developed to test the arithmetic abilities by measuring reaction time in addition to accuracy, which has barely been done in the past. Although the results showed nearly no differences in accuracy, many differences in reaction time were found. Moreover, stimulation of certain sites of the cortex resulted in an increased reaction time, although it did not interfere with accuracy. It has become clear that reaction time is a more sensitive measure than accuracy and that it is therefore important to take it into account when assessing arithmetic during direct cortical electrostimulation in patients with intractable epilepsy. This may prevent permanent postoperative calculation problems.

Introduction

In the last century, much research has been done to identify the different cognitive components involved in number processing. Many distinct cognitive models have been proposed over the years. In 1992, Dehaene has presented one of the most influential models for number processing of the past, called the triple-code model. According to the authors, three main representations of numbers exist. First, numbers can be represented as a visual Arabic code, in which they are processed as identified strings of digits. Numbers can also be represented as a verbal code, in which they are processed as syntactically organized sequences of words, which makes access to rote verbal memory of arithmetic facts possible. Finally, numbers can be represented as an analogical quantity or magnitude code, in which the quantity of a given number can be retrieved and put on an internal number line, through which it gets related to other numerical quantities. Only in this quantity code semantic knowledge about numbers is processed (Dehaene, 1992; Dehaene & Cohen, 1995; Dehaene & Cohen, 1997).

According to the triple-code model, simple (single-digit) arithmetic problems can be solved through two routes: a direct and an indirect one. Through the direct route, the arithmetic problem is transcoded into a verbal representation, which can be used to retrieve information from rote verbal memory. Although arithmetic problems can be solved by completing sequences of words, this route does not process any semantic information about the numbers which are represented. Hence, it would be particularly used in overlearned problems such as simple addition and multiplication sums. On the other hand, through the indirect route the operands of an arithmetic problem are represented as quantity representations which can be manipulated. In this route semantic information about numbers is processed and therefore it would be useful whenever information from rote verbal memory is lacking, such as in subtraction and more complex calculation problems (Dehaene & Cohen, 1995; Dehaene & Cohen, 1997).

Although many other researchers agree with the triple-code model, there has been some criticism too. Chochon, Cohen, Van de Moortele, & Dehaene (1999) have argued that even in simple calculation problems often a combination of the direct route (retrieval from verbal memory) and the indirect route (quantity-based strategies) is used. This is called semantic elaboration. Semantic representations of numbers could then play a role in the retrieval of arithmetic facts as well.

Research has focused on two arithmetic operations in particular, which can be associated with the different cognitive processes described above. First, multiplication has been associated with arithmetic fact retrieval. On the other hand, subtraction has been associated with the manipulation of numerical quantities. Addition has not been studied as extensively as subtraction and multiplication, because in this arithmetic operation both numerical fact retrieval and manipulation of numerical quantity can be used (Cohen, Dehaene, Chochon, Lehéricy, & Naccache, 2000).

In addition to research on the cognitive components of number processing, there has been much interest in the neural substrate as well. Over the years, many distinct brain regions have been indicated to play a role in numerical processing, but considerable inconsistency remains. However, the idea that the parietal lobe plays an essential role in number processing is generally accepted. Most researchers agree that the intraparietal sulcus (IPS) plays a key role. It has been reported by many authors that this part of the parietal lobe is crucial for number processing and that a lesion in the IPS leads to (partial) impairments in this domain (Cantlon, Brannon, Carter, & Pelphrey, 2006; Chochon, Cohen, Van de Moortele, & Dehaene, 1999; Piazza, Izard, Pinel, & Le Bihan, 2004; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Santens, Roggeman, Fias, & Verguts, 2009). More specifically, it has been argued that particularly the horizontal segment of the intraparietal sulcus (hIPS) has to be considered to be the neural substrate of an abstract, automatic, and supramodal number representation. In a functional magnetic resonance imaging (fMRI) study it has been reported that the bilateral hIPS is activated when numbers are presented, regardless of the modality in which they are offered (visual or auditory) (Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003). Moreover, it has been shown that the activations in this brain area during explicit number manipulation are similar to the activations during number processing that requires no explicit manipulation of numbers, which has led to the suggestion that activity in the hIPS can represent both top-down (explicit number manipulation) and bottom-up (implicit number processing) mechanisms.

Other evidence is consistent with this notion. By using single-cell recordings in monkeys, Nieder & Miller (2004) have shown that groups of neurons in the posterior parietal cortex, particularly in the IPS, respond to numerosity in a number-selective way, which means that these neurons preferentially fire during the presentation of a particular numerosity. Interestingly, the results of several fMRI studies suggest that numerosity-selective neurons are also present in the human IPS (Cantlon et al., 2006; Piazza et al., 2004; Piazza et al., 2007).

In addition to the IPS, the angular gyrus (AG) has frequently been associated with number processing as well. Already in 1918, Peritz has stated that the AG would be the calculation centre of the brain. Subsequently, activations in this brain area during number processing have been reported by many authors (Dehaene et al., 2003; Delazer, Domahs, Bartha, Brenneis, Lochy, Trieb, & Benke, 2003; Gruber, Indefrey, Steinmetz, & Kleinschmidt, 2001; Ischebeck, Zamarian, Siedentopf, Koppelstätter, Benke, Felber, & Delazer, 2006; Lee, 2000) and it has become clear that a lesion (or temporary disturbance) in the AG leads to impairments in numerical processing (Barnea-Goraly, Eliez, Menon, Bammer, & Reiss, 2005; Roux, Boetto, Sacko, Chollet, & Trémoulet, 2003; Roux, Boukhatem, Draper, Sacko, & Démonet, 2009; Van Harskamp, Rudge, & Cipolotti, 2002).

In the triple-code model, ideas about the neural substrate of number processing are also proposed. Initially the model only described the functional aspects of number processing, but it has been extended with functional-anatomical information later. First, representations in the Arabic code would be localized in the bilateral inferior ventral occipito-temporal areas of the brain. The perisylvian areas in the left hemisphere would be responsible for representations in the verbal code. Finally, representations in the analogical quantity code would be localized in the bilateral inferior parietal areas (Dehaene & Cohen, 1995).

The direct and the indirect route for number processing have been associated with certain brain circuits as well. When the direct route is used, a left cortico-subcortical loop through the basal ganglia and the thalamus would be activated. When the indirect route is used, activations would be present in more brain regions. Although both hemispheres process visual information and information about numerical quantities or magnitudes, only the left hemisphere connects this information with verbal representations. Consequently, numerical information in the right hemisphere has to be transported to the left hemisphere first to connect with the verbal system. In the left hemisphere information would then be transported from the inferior parietal cortex to the left perisylvian areas (Dehaene & Cohen, 1995; Dehaene & Cohen, 1997) (see Figure 1).

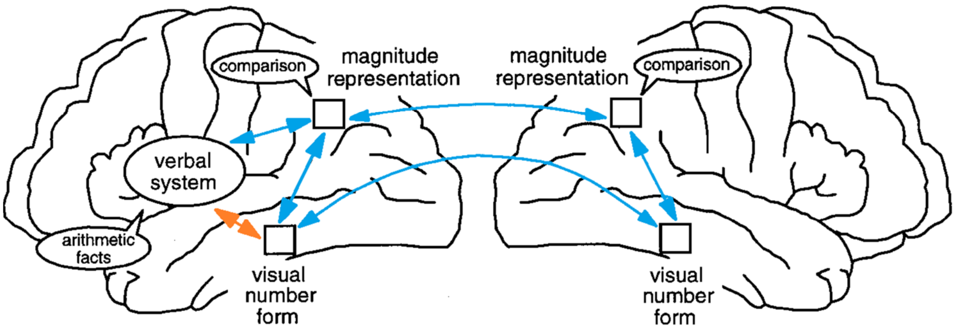


Figure 1. *Schematic representation of the triple-code model (Dehaene & Cohen, 1995). The orange arrow represents the direct route for number processing; the blue arrows represent the indirect route.*

In 2003, Dehaene, Piazza, Pinel, & Cohen have presented another anatomical model for number processing, in which they have proposed a tripartite organisation of parietal circuits (see Figure 2). First, the authors have found that activations in the hIPS increase when more quantity processing is required. This has led to the suggestion that the hIPS is domain specific and that this area functions as a core quantity system, similar to a mental number line. This system is then supplemented by two other parietal circuits, dependent on the specific task. When verbal processing is important, the left AG supports the manipulation of numbers in verbal form. This area could therefore be crucial when retrieval of facts from verbal memory is required, as in multiplication. A circuit in the bilateral posterior superior parietal lobe (PSPL) supports the attention component of number processing by orienting attention on the mental number line. Although activations in the hIPS are suggested to be specific for the number domain, activations in the other two circuits are not (Dehaene et al., 2003).

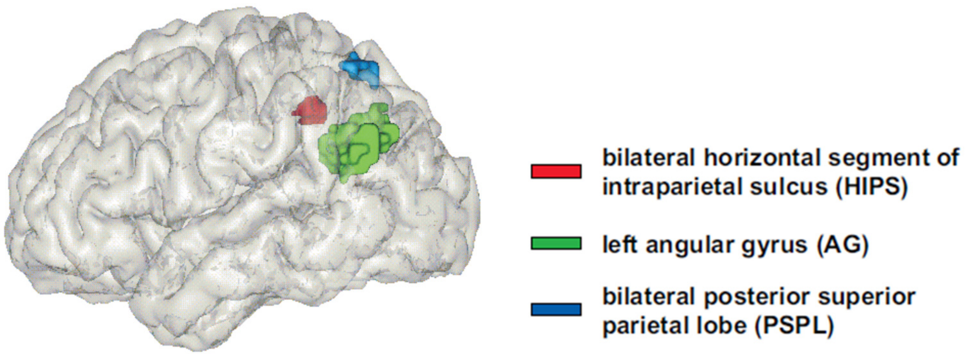


Figure 2. *Tripartite organisation of parietal brain areas involved in number processing according to Dehaene & Cohen (2003).*

Much information about the neural substrate of number processing has been derived from research on patients with brain damage. In 1918, Peritz has already examined the effects of brain damage on arithmetic. He has concluded that damage to the left hemisphere could result in an impairment in calculation, although damage in the right hemisphere could not. More recently, Dehaene & Cohen (1997) have investigated two acalculic patients with lesions in different brain areas. One of them suffered from a right inferior parietal lesion and showed domain-specific impairments which only affected numerical quantity manipulation, sparing automatized fact retrieval. The other patient, who suffered from a left subcortical lesion, showed deficits in the retrieval of facts from verbal memory, both in number processing and in non-numerical domains. On the other hand, manipulation of numerical quantities was unimpaired. Based on this double dissociation, the authors have concluded that the bilateral inferior parietal lobe is activated during numerical quantity manipulation and that the left cortico-pallido-thalamic loop is activated during simple arithmetic fact retrieval. However, a few years later the authors have argued that there are in fact three different categories of impairments in number processing: domain-specific semantic impairments following lesions in the IPS, impairments of fact retrieval from verbal memory due to lesions in the left perisylvian areas (including the AG), and impairments of spatial attention on the mental number line following lesions in the dorsal parietal attention system (Dehaene & Cohen, 2003).

Results from studies on acalculic patients have led to contradictory results as well. Although Lee (2000) has reported a patient who showed impaired multiplication and intact subtraction after a lesion including the left AG and supramarginal gyrus (SMG), Van Harskamp et al. (2002) have described a patient with a lesion in the same brain area, resulting in the complete opposite outcome (intact multiplication and impaired subtraction).

As described above, much research has been done on arithmetic and the brain. Most studies on this subject have used fMRI. However, a disadvantage is that most non-invasive techniques do not differentiate between areas which are really essential for calculation and areas which are only involved in it (Duffau, Denvil, Lopes, Gasparini, Cohen, Capelle, & Van Effenterre, 2002). A technique which differentiates between indispensable and less essential areas is direct cortical electrostimulation. During direct cortical electrostimulation, activity in small parts of the cortex is temporarily disrupted. When the cortex is stimulated during the execution of a task, it becomes clear which brain areas are essential for the tested function because stimulation of these areas results in transient functional impairments. This is called functional mapping and is frequently applied during resective surgery in patients with brain tumours or intractable epilepsy. Often language and visuomotor functions are tested, but only few studies have applied electrostimulation to examine which brain regions are essential for arithmetic.

Whalen, McCloskey, Lesser, & Gordon (1997) have reported that electrostimulation in one small area of the left anterior parietal cortex disrupts single-digit multiplication, which has led to the conclusion that this part of the left parietal lobe is important for arithmetic fact retrieval. In another study calculation mapping was applied during the resection of a glioma in a left parieto-occipital region including the AG. The authors have reported that stimulation disrupted calculation on three sites, all located within the left anterior AG. In the inferior part of the AG stimulation only disrupted multiplication, in the superior part of the AG (below the IPS and behind the SMG) stimulation only disrupted subtraction, and in the site between these areas both arithmetic operations were disrupted during stimulation. Based on these results, the authors have suggested that the AG can be considered to be a calculation centre in the brain (Duffau et al., 2002), which is consistent with the idea of Peritz (1918).

In another electrostimulation study multi-digit addition was tested. Simple (single-digit) addition and multiplication were not examined because the authors wanted to rule out automaticity (Roux et al., 2003). The authors have reported that stimulation of the AG resulted in calculation impairments in all tested patients and that stimulation of sites near the IPS (and also once stimulation of the SMG) sometimes disrupted calculation too. Roux et al. (2009) have found interference sites in three brain regions: in the AG, near the IPS, and in area F2 (frontal lobe). The authors have argued that although the consequences of acalculia are variable, this disorder has a negative impact on the social and professional life of the patients. Researchers agree that it is therefore very important to use calculation tasks during functional mapping in the dominant parietal lobe (Roux et al., 2009) and more specifically near the IPS (Roux et al., 2003) and the AG (Duffau et al., 2002; Roux et al., 2003). In this way permanent postoperative acalculia can be prevented.

In the current study direct cortical electrostimulation has been used to investigate which brain areas are involved in calculation by testing patients with intractable epilepsy, who had been selected for brain surgery. Arithmetic has been mapped to make sure that the neurosurgical intervention would not lead to postoperative acalculia. As the investigation was primarily for clinical purposes, stimulation has been localized particularly surrounding the epileptic focus. Only multiplication and subtraction have been tested, both at two different levels. Addition has not been investigated, since both numerical fact retrieval and manipulation of numerical quantity can be involved in this arithmetic operation. Neither division has been studied, because this operation seems to require similar mechanisms as multiplication (Lee, 2000).

So far, electrostimulation studies on arithmetic have focused on the number of errors that patients make during stimulation. However, additional information may be gained from reaction times. It has been demonstrated before that some patients with brain lesions are still able to perform calculation problems accurately, however abnormally slowly (Duffau et al., 2002). This slowness could result from the fact that other strategies have to be used than before the lesion, which takes extra time. For instance, when numerical fact retrieval from verbal memory is impaired, multiplication problems have to be solved by manipulating numerical quantities (Dehaene & Cohen, 1997). It is therefore very important to record reaction times next to accuracy: when testing accuracy only, postoperative calculation problems can be overlooked. Hence, the current study has measured reaction times as well as accuracy.

Methods

Case presentation

Case 1 – N.V.

N.V., a 33-year old woman with a history of epilepsy since age 4, was admitted for neurosurgical relief of intractable seizures. On average N.V. had 3 to 4 complex partial seizures and 1 to 5 absences every day. Language representation was left-sided (Wada-test). Registration of EEG showed that the ictal onset zone was located in the left frontal lobe, adjacent to a dysplasia (type II B). Preoperative neuropsychological examination has shown earlier that the intelligence level of N.V. was below average (total IQ: 75).

Case 2 – M.B.

M.B., a 28-year old man with a history of epilepsy since age 13, was admitted for neurosurgical relief of intractable seizures as well. When M.B. was 3 years old he had a resection of a low-grade glioma in the left parasagittal parietal lobe. On average M.B. had 3 partial seizures a day. Less frequently he had cluster seizures too. Preoperative neuropsychological assessment has previously shown impairments in visual (working) memory and phonological fluency. Mild impairments were found in visual perception (shape and colour detection) and tactile perception, and signs of mild ideational apraxia have been reported. These impairments have been associated with the parasagittal parietal lesion.

Control group

A control group has been used to evaluate the arithmetic performances of the patients. The group consisted of 8 different subgroups, which were grouped based on 3 variables: gender (man/woman), age (18-30/31-46), and level of education. The education level has been determined according to the categorization system of Verhage (1964) (education level ≤ 5 = primary school education, lower high school education or lower professional education; education level 6-7 = higher high school education, higher professional education or academic education). All subgroups consisted of 10 participants, except for the group of women with age 31-46 and education level ≤ 5, which consisted of 9. Consequently the whole control group consisted of 79 participants. The different subgroups were as follows: men with age 18-30 and education level ≤ 5; men with age 18-30 and education level 6-7; men with age 31-46 and education level ≤ 5; men with age 31-46 and education level 6-7; women with age 18-30 and education level ≤ 5; women with age 18-30 and education level 6-7; women with age 31-46 and education level ≤ 5; women with age 31-46 and education level 6-7. The results of the control group were used to create standardized norms for the new arithmetic task, which will be described in the next section.

Materials

Arithmetic task

To test arithmetic a new digital task has been developed using E-Prime software (version 1.1).

This task consisted of 4 different blocks, based on 2 variables: arithmetic operation (subtraction/multiplication) and level of difficulty (lower level/higher level). The meaning of these levels will be further explained later. The different blocks were as follows: lower-level subtraction sums, higher-level subtraction sums, lower-level multiplication sums and higher-level multiplication sums. These blocks were offered to all participants in this order. Each block consisted of 5 practice sums and 20 test sums. Each block of subtraction sums was preceded by subtraction practice sums, which were identical for both levels. The multiplication blocks started with multiplication practice sums, which were also the same for both levels. The level of the practice sums was very basic, for example 6-2 for subtraction and 3x1 for multiplication.

The arithmetic task was presented on a computer screen (15″) on which all text was shown in black letters on a white background. The participants could type their answers on a separate keypad. The first block, lower-level subtraction, started with the presentation of the instructions of the task on the computer screen. After reading the instructions, the subjects had the opportunity to ask for further explanation when necessary. When everything was clear, the first practice trial was started. Each trial started with the presentation of a small fixation cross (+) in the centre of the screen. When the researcher clicked the left mouse button, the first practice sum appeared. The participants were instructed to solve all sums as quickly as possible. They were also instructed to hit the ENTER button on the keypad as soon as they had solved the calculation problem. The time allowed to solve the sums was infinite. When the ENTER button was hit, the presented sum disappeared immediately and only the white background was shown. The participant subsequently entered the answer on the keypad. When someone made an error while typing the answer, the researcher immediately asked him/her to give the answer verbally. 2000 ms after the participant hit the ENTER button, the next trial started, also when the participant had not (yet) typed an answer. This was done to prevent participants from hitting the ENTER button and subsequently solving the sum. The fixation cross was presented again and everything was repeated until the practice trials were finished. Subsequently, instructions appeared on the screen again and the participants were told that the test trials were about to start and that those would be more difficult than the practice trials. They were asked if everything was clear, and if not, they could get further explanation from the researcher. Within each block, the test trials were presented in random order.

The lower-level subtraction sums consisted of two-digit minus one-digit numbers, such as 84-5. The two-digit numbers ranged from 27 to 95 and the single-digit numbers ranged from 2 to 7. At this level, the correct answer was in the same decade as the two-digit number of the sum. The higher-level subtraction sums also consisted of two-digit minus one-digit numbers, but in these sums the correct answer was not in the same decade as the two-digit number of the sum, such as 53-6. At this level, the two-digit numbers ranged from 26 to 95 and the single-digit numbers ranged from 3 to 9. The lower-level multiplication sums consisted of one-digit times one-digit numbers, such as 3x6. At this level, one of the single-digit numbers was always 2, 3 or 4. The higher-level multiplication sums also consisted of one-digit times one-digit numbers, but at this level both numbers of the calculation problems were higher than 4, such as 7x8. All calculation problems (both practice sums and test sums) are shown in Appendix 1.

For each participant, both accuracy and reaction times were logged. When the participants gave the correct answer verbally after making a typing error, this was still interpreted as a correct response. However, verbal answers were only accepted when they were given immediately after the typing error was made, to prevent that the participants could solve the sum after they had hit the ENTER button. The reaction time of a trial was measured from the moment of the presentation of the sum on the computer screen until the moment that the participant hit the ENTER button.

<u>Electrostimulation</u>

In both patients a subdural grid of electrodes was implanted to apply direct cortical electrostimulation. The inter-electrode distance was 1 cm and the diameter of the electrodes was 4 mm. Stimulation was applied with an electrical stimulator of Micromed, with monofasic pulses of 300 and 1000 μs in a frequency of 50 Hz. In patient N.V. the stimulation interval was set at 4 seconds and an amplitude of 4 or 7 mA. During calculation mapping, stimulation was started simultaneously with the presentation of a sum on the computer screen.

In patient N.V. calculation was mapped extensively. However, for patient M.B. calculation could unfortunately not be mapped. Due to complications this patient had to undergo surgery 3 days earlier than originally planned. As functions of highest clinical relevance (such as language and visuomotor functions) were examined first, there was no time left for calculation mapping. Descriptions of the effect of electrostimulation on arithmetic will therefore be based on the results of patient N.V. only.

Procedure

<u>Preoperative measures</u>

One day before the implantation of the subdural electrodes, both patients were tested preoperatively on the arithmetic task. Because of the overall slowness of patient N.V. (which also appeared during the examination of her information processing speed), only the lower-level sums were used for this patient. Although she might have been able to solve the higher-level sums too, it would probably take her too much time to be useful during electrostimulation (which can only be applied for a short continuous period of a few seconds). Moreover, N.V. was allowed to take more time to type the answers on the keypad (5000 ms instead of 2000 ms). However, this did not affect her reaction times, since those were based on the time it takes to solve the sum and hit the ENTER button, which precedes the moment of typing the answer on the keypad.

In addition to arithmetic, other cognitive domains were also tested preoperatively during a clinical neuropsychological assessment. In patient N.V. verbal working memory (Digit Span, WAIS-III), visual working memory (Corsi Block-Tapping Task), information processing speed (Trail-Making Test, part A) and divided attention (Trail-Making Test, part B) were examined. Considerable impairments were found in visual working memory and information processing speed.

In patient M.B. both levels of subtraction and multiplication were examined. Since the other cognitive domains of this patient were tested extensively a year before, only one domain (i.e. visual perception) was examined preoperatively. No impairments were found on this domain (which was tested with a digital Line Bisection Test).

Calculation mapping

Just prior to the cortical mapping of calculation functioning, arithmetic was briefly tested without electrostimulation to investigate how the patient performed on baseline after implantation of the electrodes and with the administered medication. In patient N.V. calculation was mapped on two different days. On both days first subtraction and then multiplication was examined. The arithmetic task was offered in the same way as during the preoperative examination. However, this time the patient was allowed to give the answers verbally, because it took her too much effort to type the answers herself. When the patient started speaking, the researcher immediately hit the ENTER button and subsequently typed the given answer. The pair of electrodes that was stimulated was registered for each trial. The researcher also registered if the patient's answer was correct and whether she answered in normal speed or not.

When stimulation of a certain pair of electrodes did not interfere with calculation, a new pair of electrodes was stimulated. When stimulation did disturb calculation, the involved electrodes were stimulated again. If the answer was correct this time, the researcher concluded that stimulation of this site did not interfere with the tested arithmetic process. But when stimulation disturbed calculation a second time, this pair of electrodes was tested more extensively at the end of the examination. After all other relevant sites were stimulated, sums were offered in groups of 5 for those electrodes on which errors were made during stimulation. Stimulation was applied for 3/5 sums. In this way the effect of stimulation of these pairs of electrodes on calculation was clarified.

The location of the electrodes and which electrodes were stimulated during the different arithmetic operations is shown in Figure 3. In addition to arithmetic, verbal working memory, visual working memory and language were mapped as well.

Neurosurgery

After a week the temporarily implanted subdural electrodes were removed. In the week between the implantation and the removal of the electrodes, the epileptic focus was mapped and important functions (including arithmetic) were extensively tested. Two epileptogenic zones were localized for patient N.V. in the left frontal lobe, i.e. anterior and posterior from the dysplasia. After the removal of the grid of electrodes, a resection of the epileptic focus was performed, during which the inferior frontal gyrus and the middle frontal gyrus (including the dysplasia) were partially removed. This area is shown in Figure 4 and 5.

As mentioned earlier, in patient M.B. the resection of the epileptic focus was performed 3 days earlier than originally planned. During this neurosurgical intervention a medial superior parietal region was removed.

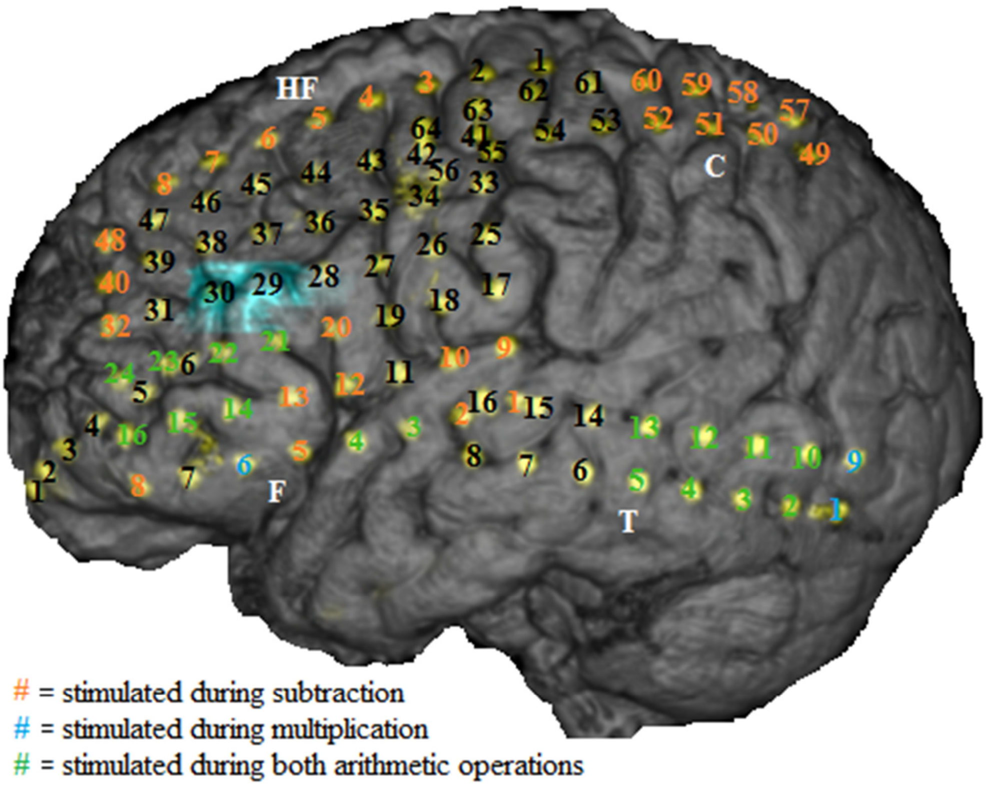


Figure 3. *MRI of patient N.V. with numbers and locations of the temporarily implanted electrodes (left hemisphere). The electrodes with orange numbers were stimulated during subtraction, the electrodes with blue numbers were stimulated during multiplication, and the electrodes with green numbers were stimulated during the examination of both arithmetic operations. Electrodes F1-6, F8-10, F 12-16 and F20-24 are situated on the inferior frontal gyrus, including Broca's area. Electrodes F32, F40 and F48 are localized on the middle frontal gyrus, and electrodes HF3-8 are situated on the superior frontal gyrus. Electrodes T1-5 and T9-13 are situated on the superior temporal gyrus, including Wernicke's area. Electrodes C49-52 and C57-60 are localized on the superior posterior parietal lobe. The blue area represents the epileptic focus.*

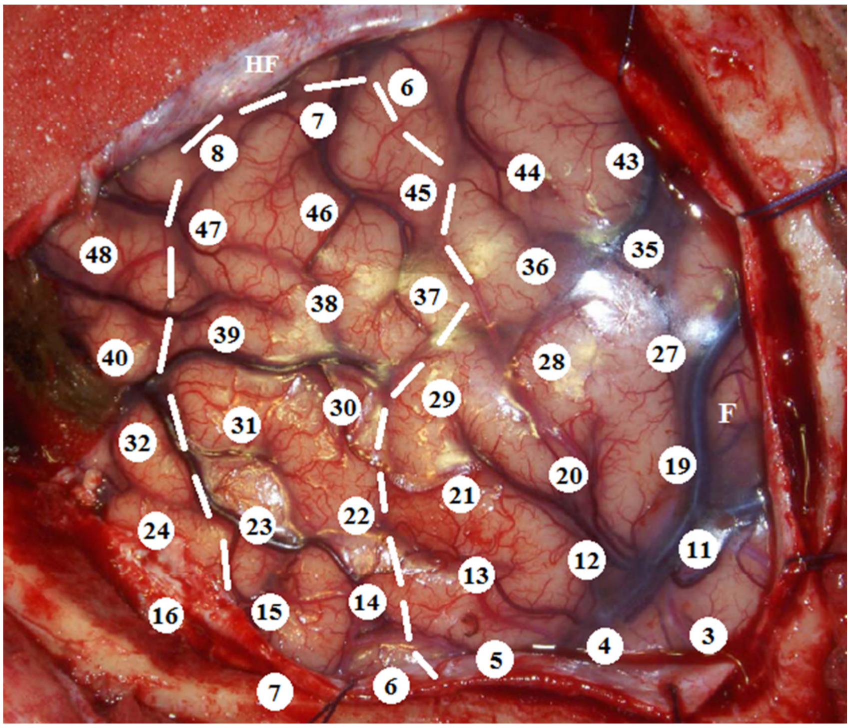


Figure 4. *Picture of the brain before the neurosurgical intervention of patient N.V. with a schematic representation of the temporarily implanted electrodes. The area within the dotted line has been removed during the resection.*

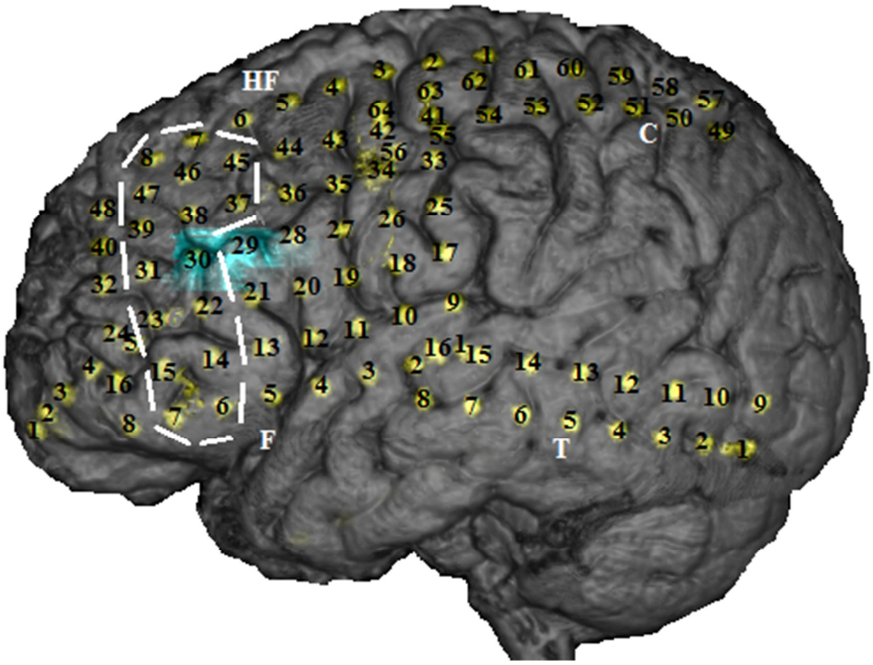


Figure 5. *MRI of patient N.V. before the neurosurgical intervention with numbers and locations of the temporarily implanted electrodes. The area within the dotted line has been removed during the resection.*

Postoperative measures

3 days after the neurosurgical intervention, the arithmetic test was repeated for both patients. In patient N.V. again only the lower-level sums were tested. In addition to arithmetic, verbal working memory and visual working memory were examined, using the same tasks as were used preoperatively. Like during the preoperative examination, considerable impairments were found in visual working memory. Moreover, mild impairments in verbal working memory were found this time.

For patient M.B. only lower-level subtraction was examined postoperatively. Because many other cognitive domains were examined, there was no time left to examine the arithmetic abilities more extensively. In addition to calculation, verbal working memory, visual working memory and visual perception were tested again, using the same tests as were used preoperatively. Naming (Boston Naming Test), language comprehension (Token Test, short form), episodic memory (Verbal Paired Associates, WMS-III), visuomotor functioning (pointing), and apraxia (Lezak's Apraxia Test, Goldenberg's Ideomotor Apraxia Test) were examined as well. Again impairments in visual working memory and signs of mild ideational apraxia were found. In addition to these impairments also mild impairments in visuomotor functioning were found postoperatively.

Analyses

In this study two parameters were used as dependent variables: accuracy and reaction time.
With respect to accuracy, an answer could be correct or incorrect. Incorrect answers and trials with no answer were both interpreted as errors. The second variable, reaction time, can be defined as the time it takes to solve the sum. As mentioned earlier, reaction times were measured from the moment of the presentation of the sum until the moment that the participant hit the ENTER button.

The results were analysed using several statistical tests. First, the results of the control group were statistically tested with an analysis of variance (ANOVA). By using this test, the accuracy and the reaction times of the different subgroups were compared. Gender, age and level of education were used as independent variables.

The results of the patients were compared to the results of the control group with a modified t-test. This t-test can be used to compare an individual's test score against norms derived from small samples (Crawford & Howell, 1998). The preoperative and postoperative results of the patients were compared to the results of the matching control subgroup, to examine if the arithmetic abilities of the patients before and after surgery differed significantly from the arithmetic abilities of healthy participants with the same gender, age and education level.

The preoperative and postoperative results of the patients were compared by using two different tests. First, a chi-square test was used to compare the preoperative and postoperative accuracy. Second, an independent samples t-test was used to examine if the reaction times of the patients after surgery differed significantly from their own preoperative reaction times.

To examine possible differences in accuracy between the trials with stimulation and the trials without stimulation a chi-square test was used. By using this test, the proportion of correct answers of trials with stimulation was compared to the proportion of correct answers of trials without stimulation. To compare the reaction times of stimulation trials with the reaction times of non-stimulation trials, means and standard deviations of non-stimulation trials were used as baseline. When the reaction times during stimulation trials deviated more than 2 standard deviations from the mean reaction time on baseline, they were interpreted as significantly different. For this analysis only reaction times of correct trials were used.

PASW Statistics software (version 18, SPSS Inc.) was used for the ANOVA, chi-square test and independent samples t-test. A software programme named Singlims_ES was used for the modified t-test (Crawford, Garthwaite, & Porter, 2010).

Results

Control group

Accuracy

To investigate the influence of gender, age and education level on accuracy and reaction time, the results of the different control subgroups were compared. Although no significant differences in accuracy between men and women were found at $\alpha = 0.05$, the difference between men and women for higher-level multiplication is marginally significant ($F(1,77) = 3.43$, $p = 0.07$), with a higher accuracy for the male participants. The results are shown in Table 1. No significant differences in accuracy between younger (18-30 yrs.) and older (31-46 yrs.) participants were found. These results are shown in Table 2. Only for lower-level multiplication a significant difference in accuracy between lower educated and higher educated participants was found. The accuracy of the higher educated participants appeared to be significantly higher than the accuracy of the lower educated participants ($F(1,77) = 4.99$, $p = 0.03$). For all other subtasks no significant differences were found. The results are shown in Table 3. Finally, there was no significant interaction between gender, age and education. These results are shown in Table 4.

Table 1. *Accuracy results for men and women for all subtasks and the results of the ANOVA.*

	Accuracy				
	M (SD) men	M (SD) women	F	df	Sig. (two-tailed)
LL subtraction	19.1 (1.2)	18.9 (1.4)	0.61	1, 77	0.44
HL subtraction	18.2 (1.6)	17.8 (2.3)	0.84	1, 76	0.36
LL multiplication	19.5 (0.8)	19.5 (0.7)	0.27	1, 77	0.60
HL multiplication	17.7 (1.8)	16.9 (2.4)	3.42	1, 77	0.07*

LL = lower-level, HL = higher-level

* marginally significant

Table 2. *Accuracy results for younger and older participants for all subtasks and the results of the ANOVA.*

	Accuracy				
	M (SD) 18-30 yrs.	M (SD) 31-46 yrs.	F	df	Sig. (two-tailed)
LL subtraction	18.8 (1.3)	19.2 (1.2)	2.21	1, 77	0.14
HL subtraction	18.0 (1.9)	17.9 (2.1)	0.05	1, 76	0.82
LL multiplication	19.5 (0.7)	19.5 (0.8)	0.05	1, 77	0.82
HL multiplication	17.1 (2.1)	17.5 (2.2)	0.48	1, 77	0.49

LL = lower-level, HL = higher-level

Table 3. *Accuracy results for lower and higher educated participants for all subtasks and the results of the ANOVA.*

	Accuracy				
	M (SD) education ≤ 5	M (SD) education 6-7	F	df	Sig. (two-tailed)
LL subtraction	19.0 (1.3)	19.0 (1.3)	0.01	1, 77	0.93
HL subtraction	18.3 (1.9)	17.6 (2.0)	2.61	1, 76	0.11
LL multiplication	19.3 (0.8)	19.7 (0.7)	4.99	1, 77	0.03**
HL multiplication	17.4 (2.2)	17.2 (2.1)	0.24	1, 77	0.63

LL = lower-level, HL = higher-level

** significant at $\alpha < 0.05$

Reaction time

No significant differences in reaction time were found between men and women at $\alpha = 0.05$. However, the difference in reaction time for higher-level subtraction is marginally significant. The reaction times of the male participants appeared to be lower than those of the female participants ($F(1,76) = 3.51$, $p = 0.07$). The results are shown in Table 5.

Although no significant differences in reaction time were found between younger and older participants at $\alpha = 0.05$, the differences can be interpreted as marginally significant for lower-level multiplication ($F(1,77) = 3.50$, $p = 0.07$) and higher-level multiplication ($F(1,77) = 3.32$, $p = 0.07$). Interestingly, for both subtasks the mean reaction time of the older participants was lower than the mean reaction time of the younger participants. The results are shown in Table 6.

The analysis also showed marginally significant differences in reaction time between lower and higher educated participants. The mean reaction time for higher educated participants appeared to be lower than the mean reaction time for lower educated participants, both for lower-level subtraction ($F(1,77) = 2.80$, $p = 0.098$) and lower-level multiplication ($F(1,77) = 3.12$, $p = 0.08$). These results are shown in Table 7.

Table 4. *Interaction results between gender, age and education level for accuracy for all subtasks.*

	Accuracy		
	F	df	Sig. (two-tailed)
LL subtraction			
gender*age	1.20	1, 71	0.28
gender*education	0.01	1, 71	0.94
age*education	0.06	1, 71	0.81
gender*age*education	1.65	1, 71	0.20
HL subtraction			
gender*age	0.28	1, 70	0.60
gender*education	1.10	1, 70	0.30
age*education	2.19	1, 70	1.14
gender*age*education	0.23	1, 70	0.64
LL multiplication			
gender*age	2.58	1, 71	0.11
gender*education	0.16	1, 71	0.69
age*education	1.22	1, 71	0.27
gender*age*education	0.25	1, 71	0.62
HL multiplication			
gender*age	0.48	1, 71	0.49
gender*education	1.22	1, 71	0.27
age*education	0.58	1, 71	0.45
gender*age*education	0.63	1, 71	0.43

LL = lower-level, HL = higher-level

Table 5. *Reaction time (RT) results for men and women for all subtasks and the results of the ANOVA.*

	RT				
	M (SD) men (ms)	M (SD) women (ms)	F	df	Sig. (two-tailed)
LL subtraction	1392 (648)	1423 (530)	0.06	1, 77	0.82
HL subtraction	2251 (1100)	2880 (1798)	3.51	1, 76	0.07*
LL multiplication	1224 (701)	1340 (622)	0.60	1, 77	0.44
HL multiplication	2668 (2270)	3378 (3107)	1.35	1, 77	0.25

LL = lower-level, HL = higher-level

* marginally significant

Table 6. *Reaction time (RT) results for younger and older participants for all subtasks and the results of the ANOVA.*

	RT				
	M (SD) 18-30 yrs. (ms)	M (SD) 31-46 yrs. (ms)	F	df	Sig. (two-tailed)
LL subtraction	1458 (579)	1355 (603)	0.61	1, 77	0.44
HL subtraction	2740 (1823)	2374 (1096)	1.15	1, 76	0.29
LL multiplication	1417 (682)	1143 (617)	3.50	1, 77	0.07*
HL multiplication	3561 (3105)	2462 (2163)	3.32	1, 77	0.07*

LL = lower-level, HL = higher-level

* marginally significant

Table 7. *Reaction time (RT) results for lower and higher educated participants for all subtasks and the results of the ANOVA.*

	RT				
	M (SD) education level ≤ 5 (ms)	M (SD) education level 6-7 (ms)	F	df	Sig. (two-tailed)
LL subtraction	1518 (628)	1299 (535)	2.80	1, 77	0.098*
HL subtraction	2596 (1235)	2520 (1739)	0.05	1, 76	0.83
LL multiplication	1413 (735)	1154 (561)	3.12	1, 77	0.08*
HL multiplication	3371 (3040)	2675 (2358)	1.30	1, 77	0.26

LL = lower-level, HL = higher-level

* marginally significant

Finally, a marginally significant interaction effect was found between age and education level for higher-level subtraction (F (1,70) = 3.44, p = 0.07). All interaction results are shown in Table 8. The marginally significant interaction effect for higher-level subtraction is displayed in Figure 6, showing that the reaction times of the younger participants were lower within the lower educated group, although the reaction times of the older participants were lower within the higher educated group.

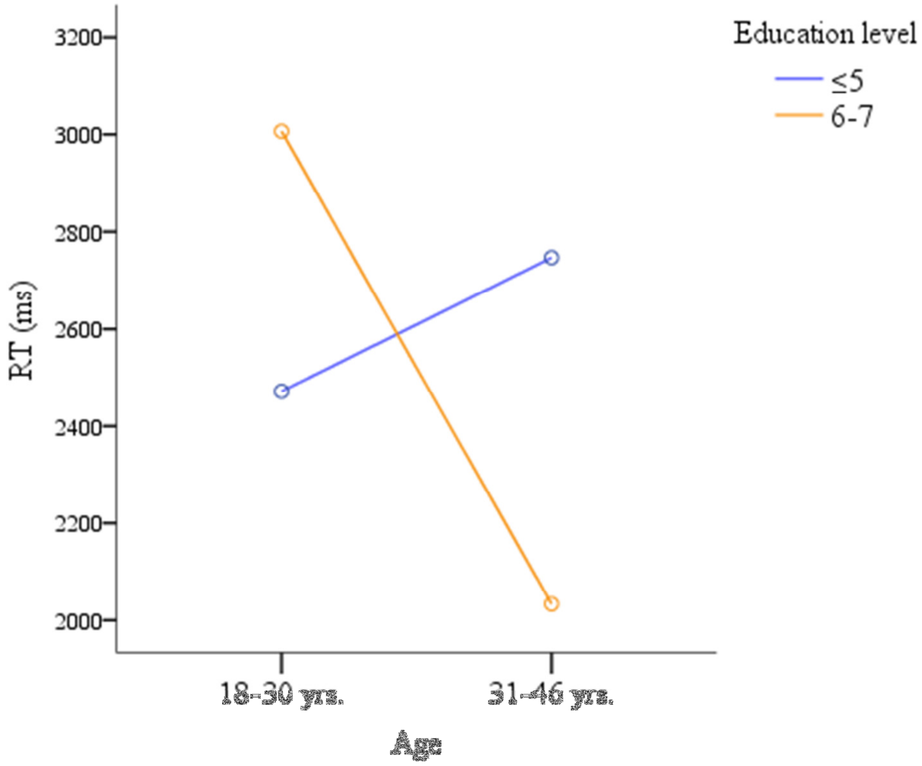
Table 8. *Interaction results between gender, age and education level for reaction time (RT) for all subtasks.*

	RT		
	F	df	Sig. (two-tailed)
LL subtraction			
gender*age	0.76	1, 71	0.39
gender*education	0.34	1, 71	0.56
age*education	1.57	1, 71	0.22
gender*age*education	0.06	1, 71	0.81
HL subtraction			
gender*age	0.35	1, 70	0.56
gender*education	0.15	1, 70	0.70
age*education	3.44	1, 70	0.07*
gender*age*education	0.39	1, 70	0.54
LL multiplication			
gender*age	1.47	1, 71	0.23
gender*education	0.43	1, 71	0.51
age*education	1.04	1, 71	0.31
gender*age*education	0.12	1, 71	0.73
HL multiplication			
gender*age	0.24	1, 71	0.62
gender*education	1.02	1, 71	0.32
age*education	2.12	1, 71	0.15
gender*age*education	0.03	1, 71	0.87

LL = lower-level, HL = higher-level

* marginally significant

Figure 6. *Interaction effect between age and education level for reaction time (RT) for higher-level subtraction.*



Norms

The results of the control group are used to create standardized norms for the digital arithmetic task which is used in the current study. These norms can be found in Appendix 2.

Patient N.V.

Patient vs. control group

The modified t-test (Crawford & Howell, 1998) showed no significant differences between the preoperative accuracy results of patient N.V. and the accuracy results of the matching control subgroup (women aged 31-46, education level ≤5). However, the test showed that the postoperative accuracy of the patient was significantly lower than the accuracy of the control subgroup for lower-level multiplication ($t = -4.53$, $df = 8$, $p = 0.001$). The postoperative results for the other subtasks (lower-level subtraction, higher-level subtraction and higher-level multiplication) did not differ significantly from the results of the control group. The results are shown in Table 9.

Interestingly, the modified t-test showed significant differences between the mean reaction time of the patient and that of the control subgroup for all subtasks and for both preoperative and postoperative results. These results are shown in Table 10.

Table 9. *Accuracy results for patient N.V. and the matching control subgroup (women aged 31-46, education level ≤5) and the results of the modified t-test (Crawford & Howell, 1998).*

	Accuracy patient N.V.	M (SD) accuracy women 31-46 yrs., education ≤ 5 (N=9)	t	Sig. (one-tailed)
LL subtraction, preop.	20	19.1 (1.4)	0.61	$p = 0.28$
LL subtraction, postop.	19	19.1 (1.4)	-0.07	$p = 0.47$
LL multiplication, preop.	18	19.3 (0.9)	-1.37	$p = 0.10$
LL multiplication, postop.	15	19.3 (0.9)	-4.53	$p = 0.001$***

LL = lower-level, HL = higher-level, preop. = preoperative, postop. = postoperative

*** significant at $\alpha < 0.01$

Table 10. *Reaction time (RT) results for patient N.V. and the matching control subgroup (women aged 31-46, education level ≤5) and the results of the modified t-test (Crawford & Howell, 1998).*

	M RT (ms) patient N.V.	M (SD) RT (ms) women 31-46 yrs., education ≤ 5 (N=9)	t	Sig. (one-tailed)
LL subtraction, preop.	3170	1452 (567)	2.87	$p = 0.01$**
LL subtraction, postop.	3597	1452 (567)	3.59	$p = 0.004$***
LL multiplication, preop.	5604	1296 (1281)	3.19	$p = 0.006$***
LL multiplication, postop.	8044	1296 (1281)	5.00	$p = 0.001$***

LL = lower-level, HL = higher-level, preop. = preoperative, postop. = postoperative

** significant at $\alpha < 0.05$

*** significant at $\alpha < 0.01$

Preoperative vs. postoperative results

For lower-level subtraction, the proportion of correct answers was 20/20 during the preoperative examination and 19/20 during the postoperative examination. Chi-square analysis showed no significant difference between these proportions (χ^2 (1, N = 40) = 1.03, p = 0.50). For lower-level multiplication, the proportion of correct answers was 18/20 during the preoperative examination and 15/20 during the postoperative examination. Again chi-square analysis reported no significant difference between these proportions of correct answers (χ^2 (1, N = 40) = 1.56, p = 0.20).

The preoperative mean reaction time for lower-level subtraction was 3170 ms and the postoperative mean reaction time was 3597 ms. An independent samples t-test showed a marginally significant difference between these reaction times (t = -1.52, df = 38, p = 0.07, one-tailed). The results are shown in Figure 7. The preoperative mean reaction time for lower-level multiplication was 5604 ms and the postoperative mean reaction time was 8045 ms. Again a marginally significant difference (t = -1.60, df = 32, p = 0.06, one-tailed) was found. These results are shown in Figure 8.

Figure 7. Mean reaction time (RT) for patient N.V. for preoperative and postoperative lower-level subtraction.

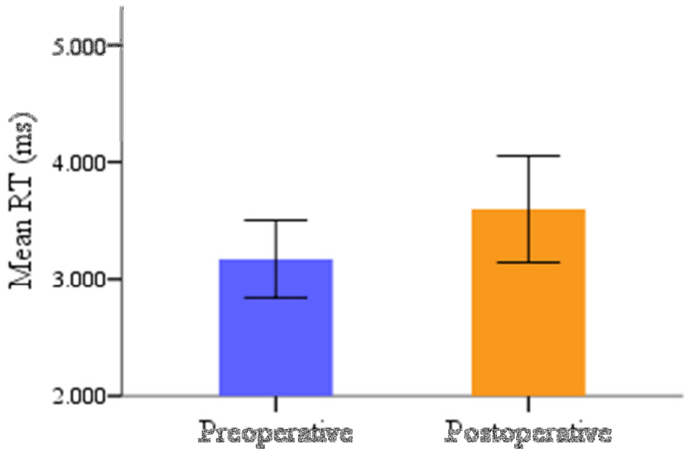
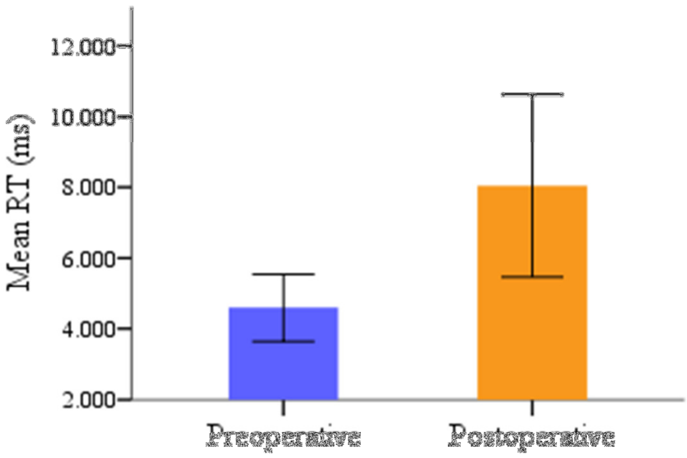


Figure 8. Mean reaction time (RT) for patient N.V. for preoperative and postoperative lower-level multiplication.



Direct cortical electrostimulation

When looking at the results of electrostimulation, stimulation of two pairs of electrodes (F12-13 and T12-13) suggested interference with subtraction. However, chi-square analysis reported no significant differences between the accuracy of stimulation trials and that of non-stimulation trials for electrodes F12-13 (χ^2 (1, N = 8) = 0.38, p = 0.75) and T12-13 (χ^2 (1, N = 8) = 0.47, p = 0.71). Stimulation of several sites suggested interference with multiplication as well. However, chi-square analyses again showed no significant differences between the accuracy of stimulation and non-stimulation trials. The results are shown in Table 11.

The mean reaction time for lower-level subtraction on baseline was 2865 ms and the standard deviation was 666 ms. Consequently the cut-off score was 4197 ms (M + 2 SD). Stimulation of electrodes F3-4, F14-22 and C50-51 resulted in significantly higher reaction times (>2 SD) for subtraction compared to baseline. These results are shown in Table 12. The localization of these electrodes is shown in Figure 9. The mean reaction time for lower-level multiplication on baseline was 5909 ms and the standard deviation was 4191 ms. Consequently the cut-off score was 14291 ms. Stimulation did not result in significantly higher reaction times for multiplication.

Table 11. *Accuracy results for stimulation and non-stimulation trials for electrodes with incorrect answers for lower-level multiplication during stimulation and the results of the chi-square analyses.*

	Stimulation		No stimulation		Chi-square test (df=1)	
Electrodes	Number of trials	Number of correct trials	Number of trials	Number of correct trials	χ^2	Sig. (one-tailed)
F6-15	3	2	2	1	0.14	$p = 0.70$
F15-16	2	1	2	2	1.33	$p = 0.50$
F22-23	4	3	2	2	0.60	$p = 0.67$
T1-2	4	3	2	2	0.60	$p = 0.67$
T3-4	1	0	2	2	3.00	$p = 0.33$
T2-10	4	2	2	0	1.50	$p = 0.40$
T9-10	5	4	2	1	0.63	$p = 0.52$
T10-11	4	3	2	2	0.60	$p = 0.67$
T12-13	4	2	2	2	1.50	$p = 0.40$

Table 12. *Mean reaction time (RT) on baseline and significantly higher (>2 SD) reaction times for lower-level subtraction during stimulation of the different pairs of electrodes.*

		RT (ms)			
M baseline	SD baseline	Cut-off score	F3-4	F14-22	C50-51
2865	666	4197	5498	6153	4306

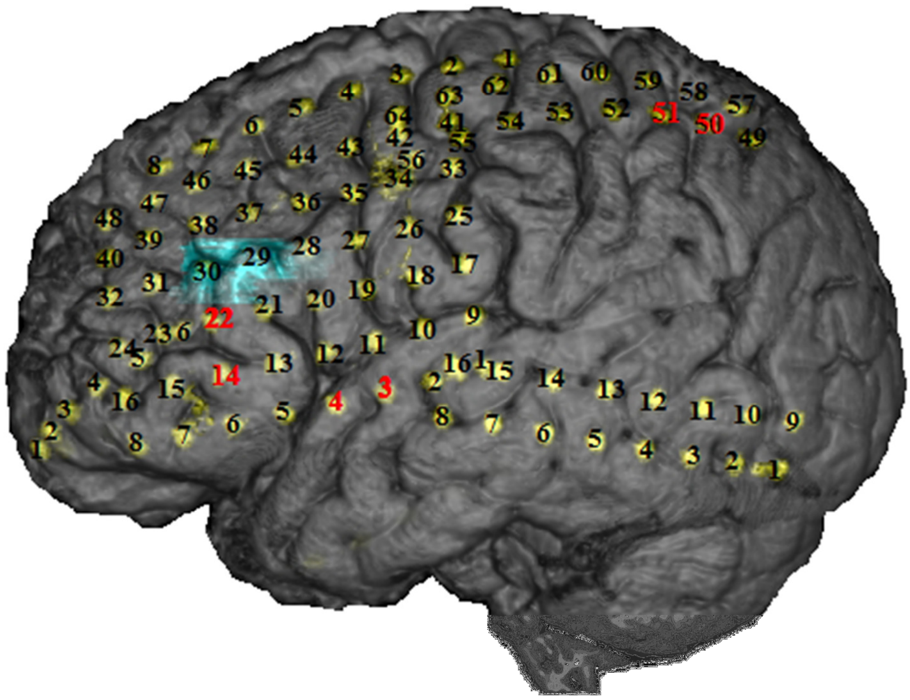


Figure 9. *MRI of patient N.V. with numbers and locations of the temporarily implanted electrodes. The sites where stimulation resulted in significantly higher reaction times for lower-level subtraction are indicated in red.*

<u>Working memory</u>

In addition to arithmetic, working memory has been investigated. Although both verbal and visual working memory can be involved in arithmetic, visual working memory is more relevant for the current digital arithmetic task. Stimulation of two sites of the cortex interfered with visual working memory, i.e. one site on the inferior frontal gyrus (electrodes F13-14) and one site on the superior temporal gyrus (electrodes T10-11).

<u>Language</u>

Language has been investigated during electrostimulation as well. Stimulation of several sites on the inferior frontal gyrus (electrodes F19-20, F20-21 and F21-29) and some sites on the middle frontal gyrus (electrodes F35-36 and F42) interfered with speech production.

Patient M.B.

<u>Patient vs. control group</u>

The modified t-test (Crawford & Howell, 1998) showed no significant differences between the accuracy results of patient M.B. and the accuracy results of the matching control subgroup (men aged 18-30, education level 6-7). The results for all subtasks are shown in Table 13. Significant differences between the mean reaction time of the patient and that of the control subgroup were found for lower-level subtraction, both for the preoperative ($t = 1.89$, $df = 9$, $p = 0.045$) and the postoperative ($t = 2.95$, df = 9, p = 0.008) examination. The analyses showed no significant differences for higher-level subtraction, lower-level multiplication and higher-level multiplication (see Table 14).

Table 13. *Accuracy results for patient M.B. and the matching control subgroup (men aged 18-30, education level 6-7) and the results of the modified t-test (Crawford & Howell, 1998).*

	Accuracy patient M.B.	M (SD) accuracy men 18-30 yrs., education 6-7 (N=10)	t	Sig. (one-tailed)
LL subtraction, preop.	17	18.5 (1.5)	-0.95	$p = 0.18$
LL subtraction, postop.	18	18.5 (1.5)	-0.32	$p = 0.38$
HL subtraction, preop.	18	18.2 (1.5)	-0.13	$p = 0.45$
LL multiplication, preop.	19	19.5 (0.7)	-0.67	$p = 0.26$
HL multiplication, preop.	17	17.6 (1.4)	0.20	$p = 0.42$

LL = lower-level, HL = higher-level, preop. = preoperative, postop. = postoperative

Table 14. *Reaction time (RT) results for patient M.B. and the matching control subgroup (men aged 18-30, education level 6-7) and the results of the modified t-test (Crawford & Howell, 1998).*

	M RT (ms) patient M.B.	M (SD) RT (ms) men 18-30 yrs., education 6-7 (N=10)	t	Sig. (one-tailed)
LL subtraction, preop.	2674	1336 (674)	1.89	$p = 0.045$**
LL subtraction, postop.	3417	1336 (674)	2.95	$p = 0.008$***
HL subtraction, preop.	4392	2424 (1587)	1.18	$p = 0.13$
LL multiplication, preop.	1387	1144 (848)	0.27	$p = 0.40$
HL multiplication, preop.	4040	3389 (5129)	0.12	$p = 0.45$

LL = lower-level, HL = higher-level, preop. = preoperative, postop. = postoperative

** significant at $\alpha < 0.05$

*** significant at $\alpha < 0.01$

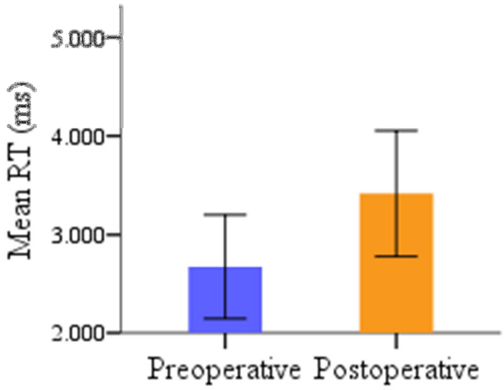
Preoperative vs. postoperative results

Since only lower-level subtraction was tested postoperatively for this patient, only the preoperative and postoperative results of this subtask were compared. The proportion of correct answers was 17/20 during preoperative testing and 18/20 during postoperative testing. Chi-square analysis showed no significant difference between the preoperative and postoperative accuracy (χ^2 (1, N = 40) = 0.23, p = 0.50). An independent t-test showed that the postoperative mean reaction time was significantly higher than the preoperative mean reaction time (t = -1.80, df = 38, p = 0.04, one-tailed). This result is shown in Figure 10.

Working memory

Working memory has been tested for patient M.B. as well. Stimulation of several sites of the cortex interfered with visual working memory, i.e. electrodes P11-19, P17-18, P18-19, P19-20, P20-21, P19-26, P19-27, P20-27, HC50-51, and HC57-58. These sites were all situated on the superior parietal lobe. The locations of the different electrodes are shown in Figure 11.

Figure 10. Mean reaction time (RT) for patient M.B. for preoperative and postoperative lower-level subtraction.



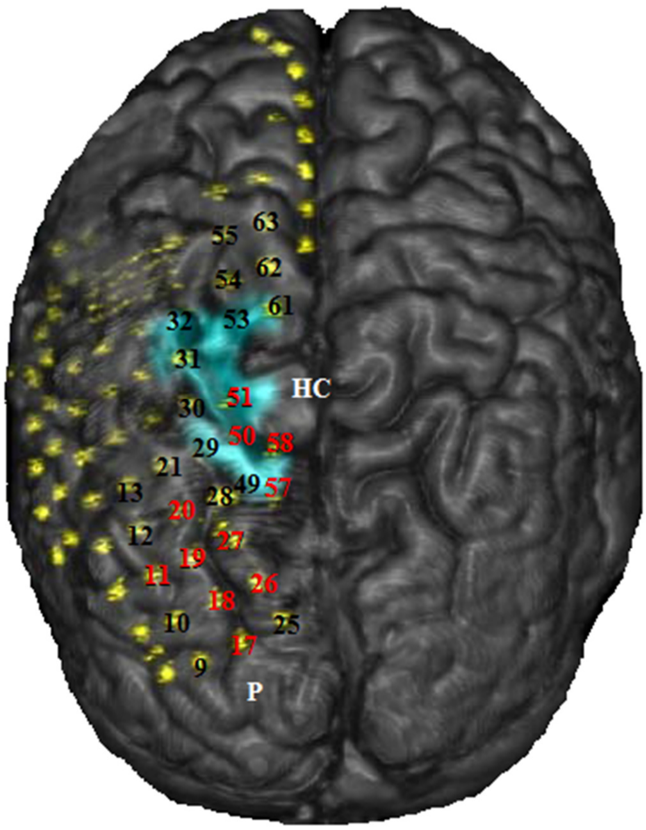


Figure 11. *MRI of patient M.B. with numbers and locations of the temporary implanted electrodes (left hemisphere). The red numbers indicate the sites where stimulation interfered with visual working memory.*

Discussion

The current study aimed to assess arithmetic processes in two patients with intractable epilepsy who had been selected for resective neurosurgery. Arithmetic was assessed preoperatively, postoperatively, and during direct cortical electrostimulation. A new digital arithmetic task has been developed which not only recorded accuracy, but also reaction time. The current study aimed to investigate the effect of electrostimulation on reaction time, as this has barely been studied in the past. Another aim of the study was to examine the differences between the preoperative and postoperative performances of the patients. In addition to the patients, a control group was tested as well, which made it possible to compare the performances of the patients with those of healthy participants. Moreover, the influence of gender, age and education level on arithmetic abilities were investigated and standardized norms for the arithmetic task were created based on the results of the control group.

With respect to the control group, several differences were found. The accuracy of the male participants was higher than that of the female participants during higher-level multiplication, although this difference was only marginally significant. Besides, the accuracy of the higher educated participants appeared to be higher than that of the lower educated participants for lower-level multiplication.

Comparing the reaction times, several marginally significant differences were found. The reaction times of the male participants were lower than those of the female participants for higher-level subtraction. The reaction times of the older participants were lower than those of the younger participants for lower-level and higher-level multiplication. Finally, the reaction times of the higher educated participants were lower than those of the lower educated participants for lower-level subtraction and multiplication. An interaction effect was found between age and education level for higher-level subtraction, indicating that the reaction times of the younger participants were lower within the lower educated group, although the reaction times of the older participants were lower within the higher educated group. Even though these differences are only marginally significant, the findings suggest that it is important to take into account gender, age and education level when testing calculation abilities.

The preoperative accuracy results of patient N.V. did not differ from those of the healthy participants. However, her postoperative accuracy appeared to be significantly lower than the accuracy of the matched control subgroup, at least for lower-level multiplication. The reaction times of the patient appeared to be higher than those of the healthy participants, for both lower-level subtraction and multiplication and during the preoperative and the postoperative examination.

No differences were found between the preoperative and postoperative accuracy of the patient, yet marginally significant differences were found between the preoperative and postoperative reaction times for both subtraction and multiplication. During the neurosurgical intervention the inferior frontal gyrus and the middle frontal gyrus have been partially removed. Besides, increased reaction times for lower-level subtraction were found during stimulation of two sites on the inferior frontal gyrus. These results together could indicate that the inferior frontal gyrus is involved in arithmetic, or at least in subtraction. However, the increased reaction times could be the result of a disturbance in working memory as well. The inferior frontal gyrus has been associated with number processing and arithmetic in the past, but the activations of this brain area during calculation have often been attributed to the involvement of working memory processes (Dehaene et al., 2004; Gruber et al., 2001). Unfortunately, only for one of these sites visual working memory has been tested. No disturbance of visual working memory was found during stimulation of this site, which suggests that the increased reaction time has not been caused by a disturbance in visual working memory. However, activity in the inferior frontal gyrus during number processing and arithmetic has been associated with language processes as well (Dehaene, Molko, Cohen, & Wilson, 2004; Gruber et al., 2001; Stanescu-Cosson, Pinel, Van de Moortele, Le Bihan, Cohen, & Dehaene, 2000). For patient N.V. stimulation of several sites on the inferior frontal gyrus appeared to interfere with language. Since the patient was allowed to give the answers verbally during calculation mapping, the higher reaction times could result from a disturbance in speech production. The fact that the (temporary) disturbance of the activity in the inferior frontal gyrus has resulted in calculation problems therefore may be attributable to the interference with language rather than with pure numerical or arithmetic processes. Besides, it is unclear whether the postoperative increased reaction times are an indication of a permanent slowing or just a short-term consequence of the neurosurgical intervention. Given that the differences between the preoperative and postoperative reaction times are only marginally significant, caution should be exercised anyhow.

With respect to patient M.B., the accuracy results of the patient did not differ from those of the healthy participants. However, both his preoperative and postoperative reaction times for lower-level subtraction were higher than those of the control group. No differences were found between the preoperative and postoperative accuracy of patient M.B., but also for this patient the postoperative reaction times were higher than the preoperative reaction times. This could be a consequence of the partial resection of the medial superior parietal lobe. Although this region of the parietal cortex is not frequently associated with arithmetic, there is some evidence that the superior parietal lobe is involved in numerical processing in monkeys (Sawamura, Shima, & Tanji, 2002). However, it has been argued by others that activations in this brain region during calculation reflect the involvement of visuospatial working memory and attention rather than arithmetic processes (Zago & Tzourio-Mazoyer, 2002). In fact, for patient M.B. stimulation of several sites on the medial superior parietal lobe interfered with visuospatial working memory. The higher reaction times after the resection of this area are therefore probably the result of a disturbance in working memory rather than arithmetic. Besides, the increased reaction times again may be only a short-term consequence of the surgery. To clarify this, the patients should be tested again after a few months to see to what extent the slowness in calculation was still apparent. Unfortunately, this was not possible as part of the current investigation.

In the triple-code model of Dehaene & Cohen a dissociation has been made between two routes for solving arithmetic problems: the direct route, which would be activated during the retrieval of arithmetic facts from verbal memory (as in multiplication), and the indirect route, involved in the manipulation of numerical quantities (as in subtraction) (Dehaene, 1992; Dehaene & Cohen, 1995; Dehaene & Cohen, 1997). The results of the current study suggest a dissociation between the processes involved in subtraction and multiplication as well, as the patients sometimes struggled with one of the arithmetic operations while having no problems with the other (e.g. for patient N.V. stimulation of electrodes F3-4 on the inferior frontal gyrus led to higher reaction times for subtraction sums but not for multiplication sums). At least this suggests that different processes are used during the different arithmetic operations and that these processes can be disturbed independently from each other.

As mentioned in the Introduction, particularly the intraparietal sulcus (IPS) has been indicated to play a major role in calculation and other aspects of number processing (Cantlon, Brannon, Carter, & Pelphrey, 2006; Chochon, Cohen, van de Moortele, & Dehaene, 1999; Piazza, Izard, Pinel, & Le Bihan, 2004; Piazza, Pinel, Le Bihan, & Dehaene, 2007: Santens, Roggeman, Fias, & Verguts, 2009). Several electrostimulation studies have shown that stimulation of sites on the intraparietal sulcus leads to temporary impairments in calculation (Roux et al., 2003; Roux et al., 2009). The angular gyrus (AG) is another brain region which is frequently associated with number processing and arithmetic (Barnea-Goraly et al., 2005; Dehaene et al., 2003; Delazer et al., 2003; Gruber et al., 2001; Ischebeck et al., 2006; Lee, 2000; Peritz, 1918; Van Harskamp et al., 2002). Electrostimulation studies have shown that stimulation of sites on the AG interferes with calculation as well (Duffau et al., 2002; Roux et al., 2003; Roux et al, 2009). Since the localization of the subdural electrodes has been based on the areas of most clinical relevance for patient N.V. (i.e. areas surrounding the epileptic focus), the IPS and the AG have not been investigated in the current study. Nevertheless, other areas such as the inferior frontal gyrus have been examined extensively.

Almost all previous studies on arithmetic have focused on accuracy only, without examining reaction time. Yet Duffau et al. (2002) have argued that some brain damaged patients are still able to solve calculation problems accurately, however abnormally slowly. The results of the current study are consistent with this notion. For both patients the postoperative reaction times differed from their preoperative reaction times, although accuracy did not. Consequently it would be possible for patients to have postoperative complaints about their arithmetic abilities which cannot be explained by a reduced accuracy. Besides, the current study showed that the reaction times patient N.V. and patient M.B. were at some points higher than those of healthy participants, although the patients did not make more errors. This also indicates that reaction time may be a more sensitive measure than accuracy and that it is therefore essential to take it into account. When looking at the electrostimulation results of patient N.V., stimulation of two sites on the inferior frontal gyrus and one site of the superior posterior parietal lobe resulted in higher reaction times for correct answered trials. During stimulation of these sites, the patient even answered after the stimulation interval, which demonstrates that she was not able to solve the sums during stimulation. When only accuracy had been measured, this would not be revealed.

A limitation of the current study is the fact that calculation has been mapped for only one patient. Consequently the results of this patient could not be compared to the performances of other patients, which made generalizations impossible. Since hardly any statistically grounded disturbances were found during calculation mapping, little can be concluded about the earlier suggested dissociation between the processes involved in subtraction and multiplication. Because of the fact that the IPS and the AG were not the brain areas of most clinical relevance for patient N.V., these regions were not investigated. Future research should focus on the effect of cortical electrostimulation of these brain areas on arithmetic by investigating both accuracy and reaction time in more patients, which would make it possible to compare the results of different people. In this way it will be clarified on which areas of the cortex stimulation leads to disturbances in arithmetic processes and the differences between distinct processes used in different arithmetic operations will become clear. It is then important to distinguish pure arithmetic disturbances from disturbances due to problems in language and working memory, by testing these domains extensively as well and connecting these results to the results of calculation mapping.

Another limitation of the current study is the fact that patient N.V. answered verbally during calculation mapping, although she preoperatively and postoperatively gave the answers by typing them on the keypad. This made a comparison between the calculation mapping results and the preoperative results less reliable. Besides, because of the fact that the patient was allowed to give the answers verbally, the cause of the increased reaction times was unclear, since those possibly have been influenced by difficulties in speech production. Future research should focus on typed answers, to rule out problems in the production of speech. In this way the comparison between the reaction times of the different examinations will become more reliable too, since they will all be tested in the same modality.

In the current study the number of trials for each pair of electrodes during calculation mapping was small. Due to the clinical nature of the investigation, often only three or four stimulation trials were compared to one or two non-stimulation trials. None of the observed disturbances was statistically significant. More trials should be used per electrode pair in future research, which would result in a higher statistical power and consequently an increasing probability of finding significant disturbances. This can be very helpful in clarifying the effects of electrostimulation on arithmetic.

In spite of the above mentioned limitations, the current study has contributed to the understanding of arithmetic and the brain in several ways. First of all, the results of the study demonstrate the importance of investigating reaction time when examining arithmetic abilities. It has become clear that accuracy and reaction time can be influenced separately. By looking at accuracy only, postoperative calculation problems can be overlooked.

Second, the new digital arithmetic task which was developed for the current study can be used during calculation mapping in the future. Due to the standardized norms based on healthy participants, the accuracy and reaction times of prospective patients can be evaluated easily and quickly. In this way the digital arithmetic task will contribute to the preserving of arithmetic abilities during neurosurgical interventions in patients with intractable epilepsy.

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Appendix 1: Calculation problems of the digital arithmetic task

Subtraction

Practice trials

6-3
4-2
7-4
5-3
3-1

Test trials lower-level subtraction

36-4	47-2
78-2	39-3
68-3	88-4
95-2	58-7
55-4	67-5
47-3	76-4
89-2	38-2
27-5	48-3
77-4	65-2
69-2	85-4

Test trials higher-level subtraction

36-9	44-7
73-5	32-3
66-8	87-9
95-7	53-6
51-3	64-8
46-9	71-7
82-4	36-9
26-7	45-8
74-8	63-5
63-7	82-9

Multiplication

Practice trials

1x1

2x1

3x1

1x5

4x1

Test trials lower-level multiplication

3x4	6x2
8x2	8x3
6x3	4x7
2x5	2x6
6x4	2x8
4x3	5x3
2x7	4x6
3x6	3x7
2x8	4x4
9x2	3x9

Test trials higher-level multiplication

5x8	6x8
8x6	8x5
6x9	9x7
7x7	6x6
6x7	8x9
9x5	6x5
8x7	7x6
9x8	9x9
7x5	8x8
5x9	7x8

Appendix 2: Standardized norms for the digital arithmetic task

2a. *Results and cut-off scores for accuracy and reaction time for lower-level subtraction.*

	M (SD) accuracy	Cut-off score accuracy	M (SD) reaction time (ms)	Cut-off score reaction time (ms)
Men 18-30 yrs., education ≤ 5 (N=10)	19 (1.1)	16.8	1432 (839)	3110
Men 18-30 yrs., education 6-7 (N=10)	18.5 (1.5)	15.5	1336 (674)	2684
Men 31-46 yrs., education ≤ 5 (N=10)	19.3 (1.2)	16.9	1647 (983)	3613
Men 31-46 yrs., education 6-7 (N=10)	19.7 (0.5)	18.7	1152 (481)	2114
Women 18-30 yrs., education ≤ 5 (N=10)	18.7 (1.6)	15.5	1535 (717)	2969
Women 18-30 yrs., education 6-7 (N=10)	19 (1.2)	16.6	1530 (870)	3270
Women 31-46 yrs., education ≤ 5 (N=9)	19.1 (1.4)	16.3	1452 (567)	2586
Women 31-46 yrs., education 6-7 (N=10)	18.8 (1.7)	15.4	1177 (526)	2229

2b. *Results and cut-off scores for accuracy and reaction time for higher-level subtraction.*

	M (SD) accuracy	Cut-off score accuracy	M (SD) reaction time (ms)	Cut-off score reaction time (ms)
Men 18-30 yrs., education ≤ 5 (N=10)	18 (1.7)	14.6	2229 (1426)	5081
Men 18-30 yrs., education 6-7 (N=10)	18.2 (1.5)	15.2	2424 (1587)	5598
Men 31-46 yrs., education ≤ 5 (N=10)	18.6 (1.2)	16.2	2493 (1573)	5639
Men 31-46 yrs., education 6-7 (N=10)	17.9 (2.0)	13.9	1859 (1197)	4253
Women 18-30 yrs., education ≤ 5 (N=9)	18.1 (2.8)	12.5	2715 (2222)	7159
Women 18-30 yrs., education 6-7 (N=10)	17.8 (1.8)	14.2	3590 (3506)	10602
Women 31-46 yrs., education ≤ 5 (N=9)	18.7 (2.1)	14.5	3001 (1601)	6203
Women 31-46 yrs., education 6-7 (N=10)	16.6 (2.5)	11.6	2208 (1557)	5322

2c. *Results and cut-off scores for accuracy and reaction time for lower-level multiplication.*

	M (SD) accuracy	Cut-off score accuracy	M (SD) reaction time (ms)	Cut-off score reaction time (ms)
Men 18-30 yrs., education ≤ 5 (N=10)	19.1 (0.9)	17.3	1398 (1375)	4148
Men 18-30 yrs., education 6-7 (N=10)	19.5 (0.7)	18.1	1144 (848)	2840
Men 31-46 yrs., education ≤ 5 (N=10)	19.5 (0.7)	18.1	1403 (1216)	3835
Men 31-46 yrs., education 6-7 (N=10)	19.7 (0.9)	17.9	953 (482)	1917
Women 18-30 yrs., education ≤ 5 (N=10)	19.3 (0.7)	17.9	1543 (1012)	3567
Women 18-30 yrs., education 6-7 (N=10)	20 (0)	20	1582 (1432)	4446
Women 31-46 yrs., education ≤ 5 (N=10)	19.3 (0.9)	17.5	1296 (1281)	3858
Women 31-46 yrs., education 6-7 (N=10)	19.5 (0.7)	18.1	936 (434)	1804

2d. *Results and cut-off scores for accuracy and reaction time for higher-level multiplication.*

	M (SD) accuracy	Cut-off score accuracy	M (SD) reaction time (ms)	Cut-off score reaction time (ms)
Men 18-30 yrs., education ≤ 5 (N=10)	17.4 (2.2)	13	2713 (3111)	8935
Men 18-30 yrs., education 6-7 (N=10)	17.4 (1.4)	14.6	3389 (5129)	13647
Men 31-46 yrs., education ≤ 5 (N=10)	18.1 (1.1)	15.9	2722 (4511)	11744
Men 31-46 yrs., education 6-7 (N=10)	17.3 (2.2)	12.9	1847 (2582)	7011
Women 18-30 yrs., education ≤ 5 (N=10)	16,7 (2.5)	11.7	4240 (8001)	20242
Women 18-30 yrs., education 6-7 (N=10)	17 (2.2)	12.6	3903 (6082)	16067
Women 31-46 yrs., education ≤ 5 (N=10)	16.7 (2.3)	12.1	3858 (5009)	13876
Women 31-46 yrs., education 6-7 (N=10)	17 (2.7)	11.6	1543 (1689)	4921