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Cortical stimulation on the left angular gyrus transiently disrupts addition and multiplication: two case studies.

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Abstract

Neuropsychological and neuroimaging studies strongly suggest engagement of the left angular gyrus (AG) in the efficient retrieval of verbal mathematical facts from memory. This retrieval is considered important in mental calculation taks that rely on mathematical facts, such as multiplication tables learned by heart and simple exact addition sums. Only few attempts have been made to perform corticostimulation on the AG to test this idea. The objective of this study was to infer whether temporarily disturbing the AG by corticostimulation disrupts simple exact addition and multiplication. We present two cases in which cortical stimulation of the AG transiently disrupts solving these type of sums. Stimulation of the superior parietal cortex and the occipital lobe did not reveal interference with addition and multiplication. These results are in line with the proposed function of the AG as important in calculation tasks that rely on the retrieval of mathematical facts. They also suggest the usefulness of cortical stimulation in elucidating the neural substrates of mental calculation.

Introduction

Neuroimaging studies and neuropsychological reports on brain damaged patients systematically confirm the activation of fronto-parietal networks in mental calculation (Chochon, Cohen, van de Moortele & Dehaene, 1999; Dehaene, Spelke, Pinel, Stanescu & Tsivkin 1999, Gruber, Indefrey, Steinmets, Kleinschmidt, 2001; Pesenti, Thioux, Seron & De Volder, 2000). The activation in more frontal areas has been interpreted as reflecting working memory demands (Kazui, Kitagaki & E. Mori, 2000; Zago et al., 2001) as well as error monitoring and strategic organization (Rickard et al., 2000). In the parietal lobule, two areas are identified as critical to arithmetic performance: the left angular gyrus (AG) (Chochon et al, 1999; Dehaene et al., 1999; Lee, 2000; Simon, Mangin, Cohen, Le Bihan & Dehaene, 2002; Stanescu-Cosson, Pinel, van De Moortele, Le Bihan, Cohen & Dehaene, 2000; Barnea-Goraly, Eliez, Menon, Bammer & Reiss, 2005; Gruber et al., 2001) and the bilateral horizontal segment of the intraparietal sulcus (HIPS) (Dehaene, Piazza, Pinel & Cohen, 2003; Nieder, 2005). In addition, some studies notice the involvement of the left-lateralized supramarginal gyrus (SMG) in calculation (Lee, 2000; Harskamp, Rudge & Cipolotti, 2005; Delazer & Benke 1997) (for location of these areas, see fig 1).

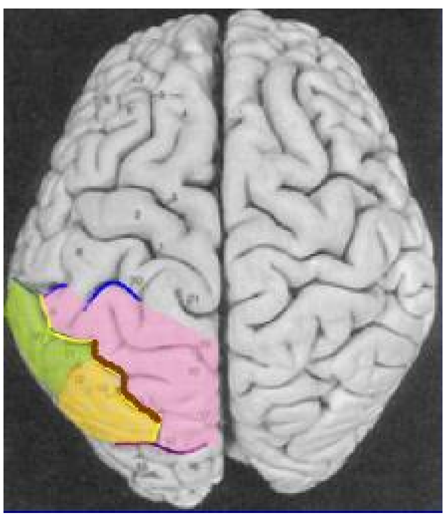


Figure 1: Brain viewed form above, top of picture is frontal. The AG (gold area) and SMG (green area) are located on the left inferior parietal cortex, separated from the postcentral sulcus by the postcentral gyrus (blue line), separated from the superior parietal cortex by the intraparietal sulcus (yellow line, brown intermediate section is the horizontal segment) and separated from the occipital lobe by the transverse occipital junction (purple line).

In an influential review of neuropsychological and fMRI studies on mental calculation, Deheane et al. (2003) build on their earlier triple code model (Dehaene et al., 1999; Dehaene & Cohen, 1997) and propose that the AG is engaged in calculations that rely on automatic and efficient retrieval of arithmetic facts in verbal memory. Insofar, calculation tasks that are learned by heart are subsumed to be mediated by the AG. The AG also shows increasingly greater activation as the task puts greater requirement on verbal processing (Dehaene et al., 2003). Therefore it is not surprising to find that the AG is also activated in several language processes such as phoneme detection (Simon et al, 2002), and digit naming (Zago et al., 2001). The AG is also associated with symptoms of Gerstmann syndrome: acalculia, finger agnosia, right/left disorientation and agraphia (Gerstman, 1940). Cortical stimulation of the AG can produce these symptoms (Roux, Boetto, Sacko, Chollet & Trémoulet, 2003). The SMG, when mentioned in the context of calculation, is mostly discussed as serving the same function as the AG, possibly a proximity effect. The SMG is in some patients associated with speech arrest (Duffau et al., 2002).

The bilateral HIPS on the other hand is put forward as a system that holds nonverbal representations of numerical quantity (Dehaene et al., 2003). It is systematically activated in all number processing tasks. (Dehaene et al., 2003; Nieder, 2005) and is increasingly activated in calculation tasks that call upon a quantitative representation of numbers (Molko et al., 2003). In that vein, calculation tasks that do not rely on automatic but on quantity manipulation are subsumed to be mediated by the HIPS. The HIPS might hold a semantic representation of numerical quantity and thus be important for numerosity (Dehaene, Molko, Cohen & Wilson, 2004). Estimating the numerosity of small set activates the right segment of the HIPS (Piazza, Mechelli, Butterworth & Price, 2002). Furthermore, the HIPS is significantly activated by auditory as well as visual numerical input when compared to letters and colors, and can thus be coined supramodal and number specific (Eger, Sterzer, Russ, Giraud & Kleinschmidt, 2003), whereas the AG seems specifically involved in the verbal modality.

Neuroimaging studies have investigated the dissociation between the AG and the HIPS. Multiplication and subtraction differentiate between number-fact retrieval and quantity manipulation according to Cohen, Dehaene, Chochon, Lehericy & Naccache (2000). Lee (2000) found that subtraction revealed more activation in the HIPS whereas multiplication revealed activation in the AG. In a case report of Cohen & Dehaene (2000), subtraction activated the right IPS, while multiplication activated predominantly left-sided parietal areas. The AG is more activated in exact than in approximate calculation while approximate calculation activates regions more in the vicinity of the HIPS (Dehaene et al,1999; Venkatraman, Ansari & Chee, 2005).

A relatively new line of research on the AG focuses on the relation between learning arithmetic facts and the AG. Even after a short training of complex calculation there is a shift from activation along the right HIPS to more activation in the AG (Ischebeck, Zamarian, Egger, Schocke & Delazer, 2007). Other studies showed a shift to activation in the AG after considerable longer training. (Delazer et al., 2003; Delazer et al., 2005, Ischebeck et al., 2006). Importantly, this shift seems to depend on the content of what is learned; trained multiplication yields more activation in the AG than subtraction. (Ischebeck et al., 2006). Furthermore, activation patterns depend on different learning strategies whereby drill training reveals more activation in the AG compared to strategy training (Delazer et al., 2005). A recent study showed stronger activation in the AG for mathematically more (as compared with less) competent individuals while solving single-digit and multi-digit multiplication problems, probably reflecting the stronger reliance on learned facts (Grabner et al., 2007). This line of research thus supports the notion of the AG as important in the retrieval of mathematic facts from memory.

Neuropsychological research has provided evidence for cases with calculation deficits who present with more or less the selective deficits in either subtraction or multiplication that are to be expected by the location of the lesion in the parietal lobule. (Delazer & Benke, 1997; Lee, 2000; Dehaene & Cohen, 1997; Cohen & Dehaene, 2000; Lampl, Eshel, Gilad & Sarova-Pinhas, 1994; Pesenti, Seron, & Van der Linden, 1994; Lemer, Dehaene, Spelke & Cohen, 2003). However, the lesions in these patients are sometimes hard to define, have different causes, are never exactly alike and cause a great variety of different functional deficits.

The dissociation seems to account for a range of selective impairments and neuroimaging evidence. However, the dichotomy is challenged by cases that do not present with deficits that were to be expected based on the described functions of the AG and HIPS. Harskamp & Cipolotti (2001) describe three cases, one with a selective impairment for simple addition, another for simple multiplication and the third for simple subtraction, while all operations are probably based on number-fact retrieval. Another case is presented who shows selective and severe impairment in multiplication, and relatively intact subtraction while the AG was spared (Harskamp et al., 2005). Still another case showed preservation of multiplication facts despite damage to the entire SMG and major part of the AG (Harskamp, Rudge & Cipolotti, 2002).

Addition has not been studied as thoroughly as multiplication and subtraction. This is probably because addition is an ambiguous operation in terms of number-fact-based or quantity based operations. Cohen et al. (2000) were the first to acknowledge the ambiguous state of addition. According to the authors, many simple addition problems like 2 + 4 are underpinned by a verbal code just like multiplication. However, more complex addition problems such as 6 + 5 can be solved through the manipulation of internal quantity representations just like subtraction. Until now, this assumption has not been confirmed. A case report of a patient with selective impairment of addition with preserved multiplication and subtraction even challenges the assumption (Harskamp et al., 2002). In a neuroimaging study of addition by Venkatraman et al. (2005), activation was found for addition not in the AG but in the bilateral anterior IPS and left posterior IPS**.** This could indicate addition is quantity based. However, for answering, two cards (one correct and one incorrect answer) were held up in the air, one on the left and one on the right side. Subjects then had to press a corresponding left or right button. In this study, the results might be influenced by the procedure since the IPS is engaged in visuomotor processing (Culham, Cavina-Pratesi & Singhal, 2006). One rTMS study on two digit plus two digit addition revealed longer RT's when stimulating the AG compared to the IPS, fitting with the assumption that addition is more number-fact based than quantity based (Göbell, Rushworth & Walsh, 2006).

Neuroimaging studies and neuropsychological case studies have been quite extensive, while only few attempts have been made to perform electrocortical stimulation on brain areas engaged in mental calculation. Neuroimaging studies provide information activation of functional areas, but are not able to differentiate these areas that are essential for the function from those 'modulatory' areas, which can be functionally compensated. Lesions in patients with calculation deficits are often gross and the precise relation between cortical areas and functional module is therefore hard to define. Electrocortical stimulation produces a stream on a small part of the cortex to temporarily disturb functioning of that area. Thereby this can reveal direct, specific and accurate evidence of functionality and can indicate the necessity of that area for the function. This method can shed new light on the cortical neural substrates associated with different calculation tasks. Whalen, McCloskey, Lesser & Gordon (1997) were the first to show that stimulation at a left parietal site impaired performance on simple multiplication problems. In a cortical stimulation study by Duffau et al. (2002), stimulation of a site on the AG immediately below the left IPS and behind the SMG disrupted subtraction and stimulation of a more inferior left angular site disrupted multiplication. This is interpreted as evidence for a double dissociation between the IPS and the AG. However, it is not known whether it is possible to induce transient disruption inside a sulcus using cortical stimulation techniques. Roux et al. (2003), in a corticostimulation study with 6 persons, found interference with two digit plus two digit addition and symptoms of Gerstmann syndrome when stimulating the AG. However, the results in these corticostimulation studies are based on observations rather than statistical analyses.

In our study, electrocortical stimulation is performed on the AG and proximate regions while the patients engages in simple exact addition and one digit times one digit multiplication. In an attempt to gain better understanding of the function of the AG we tested whether corticostimulation on the AG will disrupt solving these type of sums. The described function of the AG is not undisputed and the nature of addition is speculative. Nevertheless, considering the amount of evidence pointing towards the AG as underpinning verbal number fact-based arithmetic processes we expected that simple exact addition and multiplication will be disrupted when the AG is stimulated.

Methods:

Case presentation:

Case 1: B.S.

B.S., a 27 year old man with a history of complex generalised epilepsy since age 4 was admitted for neurosurgical relief of intractable seizures. The ictal onset zone was located at a left temporal site, probably due to multiple temporal sclerosis (MTS) (EEG, MEG). Language representation was left-sided (WADA). On neuropsychological examination his intelligence level was average (IQ=110). Preoperative testing of calculation abilities revealed that the patient was able to perform simple addition tasks (8/8 correct) and one digit times one digit multiplication (6/6 correct) within a four seconds time interval. The time interval will be discussed later on.

Case 2: A.M.

A.M., a 27 year old right handed woman with a history of epilepsy since age 8 was admitted for neurosurgical relief of intractable seizures. The ictal onset zone is left neocortical temporo-basal, however not strictly localized. Language representation was left-sided (WADA). On neuropsychological examination her intelligence level was below average (VIQ: 64; PIQ: 74). Preoperative testing of calculation abilities revealed that the patient was able to perform simple addition tasks (7/8 correct) within a five seconds time interval.

Materials

Prior to resection electrocortical stimulation was performed to delineate cortical areas with respect to function, so that the extent of the resection could be maximized without provoking cognitive impairment. Cortical stimulation parameters: bipolair, interelectrode-distance 1 cm, electrode-diameter 4 mm, pulse: monofasic, frequency 50 Hz, single pulse with a duration of 200 usec. For calculation mapping, the stimulation interval was set at four seconds and amplitude 10 mA for case B.S. and five seconds and amplitude 10 mA for case A.M.. Stimulation was applied to several different positions on the left cortex.

First, language, motor and sensorimotor functions were mapped. Then, calculation was mapped.

In patient B.S., besides the main region of interest namely the AG, other locations that are more or less proximate were also tested (fig 2). After the mapping procedure, tapes with EEG and video were used to infer response times.

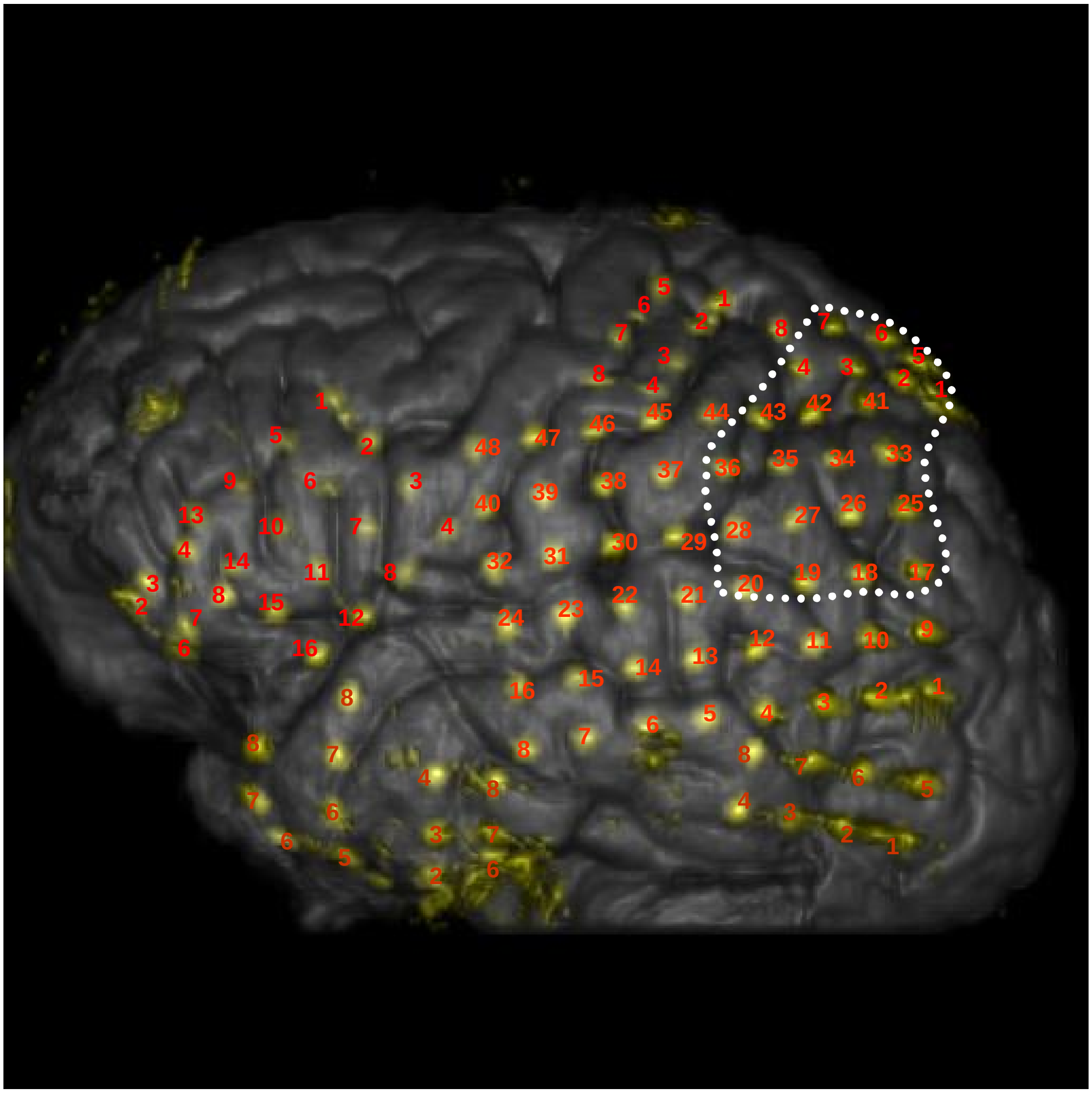
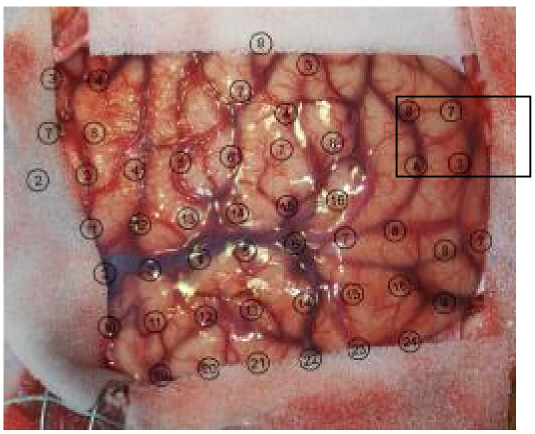


Fig (2) *MRI-image of patient B.S. with numbers and location of the temporary implanted electrodes. The yellow points within the dotted white line represent the electrodes that were stimulated during calculation tasks. Electrode 28 is situated on the angular gyrus, just posterior to the posterior ascending ramus of the sylvian fissure on Brodmann area 39. Electrodes 35, 34, 33, 27, 26, 25, 19, 18 are located on the angular gyrus as well. Electrode 20 lies on Wernicke's area, below the posterior end of the lateral sulcus. Electrode 36 and 43 are situated on the supramarginal gyrus, arching the top of the posterior ascending ramus of the sylvian fissure,* *Brodmann area 40. Electrodes 1-8 as well ass electrodes 42 en 41 are situated on the superior parietal cortex. Electrode 17 is situated on the temporo-occipital junction.*

In patient A.M. eight electrodes on the inferior parietal cortex were used for testing a possible involvement in addition tasks. The electrodes were situated in two parallel lines from the anterior side of the AG (intersection between electrodes 8-7 and 4-3) to a site more posterior on the AG (intersection between electrodes 7-6 and 3-2) to a site posterior to the transverse occipital junction on the occipital lobe
(intersection between electrodes 6-5 and 2-1) (see fig 3).



8 7 6 5

4 3 2 1

a) b)

Figure 3: a) picture of brain during implantation procedure. The square represents the tested sites for calculation, although the more posterior tested area is not visible here. b) The positioning of all the electrodes tested for calculation in two parallel lines, left is anterior and top is superior.

Procedure

The presented simple addition sums for patient B.S. all corresponded with the following properties: The sums existed of two-digits plus one-digit numerals (for example 23+9, 34+3). The magnitudes of the two-digit numeral and the answers varied from 21 to 99, respectively. The presented multiplication sums consisted of one-digit times digit sums (for example 9x8, 7x4). It was intended to present sums of equal difficulty. It was decided that the table of two would not be presented because these sums are expected to be considerably easier to solve than the other tables. All stimuli were presented verbally and not visually.

For patient A.M., only addition sums were administered. These sums were slightly different from the ones administered to patient B.S.. This was decided upon because her intelligence level was lower (VIQ: 64; PIQ: 74 < IQ=110). The sums corresponded with the following properties: The sums existed of two-digits plus one-digit numerals whereby the answer would always be within the decade (for example 22+6 or 53+4). The magnitudes of the two-digit numeral and the answers varied from 21 to 99, respectively.

The sums were administered in blocks of 5. During one block three sums were presented with stimulation and two were performed without stimulation. The stimulation was induced when the second digit was presented. The patient and experimenter were never informed when the brain was stimulated so the setup was double blind.

For patient B.S., first 45 addition blocks were presented and after that 11 multiplication blocks (see table 1, appendix 1). At each electrode, the patient performed at least one ‘addition’ block. During the multiplication trials those electrodes that revealed difficulty in addition were tested. To control for stimulation per se, some combinations of electrodes that were located on an area where interference with calculation was not expected (superior parietal cortex) were tested. The stimulation was administered on horizontal, vertical or lateral combinations of electrodes.

Patient A.M. performed at least one addition block at each above mentioned electrode. The stimulation was administered on each horizontal combination of electrodes. Then, some combinations were tested again. Some vertical combinations were also tested (see table 2, appendix 2).

Because of relatively low taxability of the patients due to extensive testing it was decided that sites that did not yield preliminary results would not be tested as often as the other sites so that the patient’s strains remained within reasonable limits.

Analyses

Case B.S.

To infer statistically whether stimulation had influence on calculation, two parameters were used as dependent variables: 1) the correctness of the answer and 2) response time (in hundreds of seconds).

The first dependent variable, correctness of an answer, was split up into two definitions: In the first definition, an answer is correct whenever the correct response is produced (the table in appendix 1 holds this definition). This means that a correct answer that is given after the stimulation interval is considered to be correct. The same holds for a correct answer given after a wrong answer. This definition of correctness is based on the assumption that everyone who is exposed to that many sums may take somewhat longer at certain sums and make some mistakes that are corrected immediately afterwards. It is possible that the stimulation induces the patients to make the mistake, which is corrected when the stimulation interval is over. Moreover, answers given after the stimulation interval may be held in working memory while stimulation makes it difficult or impossible to calculate. To account for this consideration, two analyses were performed on the first dependent variable: a) Chi-square analysis for the difference in proportion of correct answers regardless the timeframe between stimulation and no stimulation and b) Chi-square analysis for the difference in proportion of correct answers within the stimulation interval between stimulation and no stimulation. In case of the latter, a correct answer is considered incorrect when the beginning of the answer is produced after the stimulation interval. Also, in these two analyses a lack of answering in numerals is defined as incorrect rather than missing data.

The second dependent variable, the response time, is defined as the time elapsed between the moment the second numeral is produced and the moment the patient starts answering. As mentioned earlier, the response time is relevant because slowing might mean difficulty in calculation. Defining the time it takes to answer as a continue variable allows more sensitive investigation, as opposed to defining it only as a categorical variable as is the case in analysis b).

Several decisions had to be made concerning missing cases and outliers for the response time. Although the event of not producing an answer at all is probably informative for the effects of stimulation, these cases were defined as missing variables in this analysis because no timeframe could be assigned. When a correct answer was given after an incorrect answer the timeframe of the correct answer was taken into analysis. Due to the relatively long duration of some answers (e.g. answers that have been corrected by the patient) and the influence this will have on the outcome, outliers were inspected and filtered out according to the following procedure. The outliers that have been defined as missing variables for ‘response time’ and ‘correct within stimulation’ are based on explorative analysis with scatterplots and boxplots. In boxplots the 1.5 inter quartile range (1.5 IQR) criterion was inspected. Scatterplots and boxplots revealed the same outliers, so, the cases that presented as outliers in the 1.5 IQR criterion were filtered out.

The means of the response times with stimulation and without stimulation were compared with independent t-tests for every combination of electrodes and for every single electrode. This analysis was only performed for the correct items (defined as correct whenever a correct answer is given).

The tests for single electrodes are somewhat biased because these are always influenced by proximate sites. Although the validity may be somewhat limited, t-tests for tests for single electrodes have more power than t-tests for combinations of electrodes due to the higher number of cases. Therefore the analyses on single electrodes should be seen as informative exploratory results whereby the results for single electrodes could give a hint where combinations would be significant when tested more often.

Since the analysis for response time is somewhat biased by the ending of the stimulation interval, the results could be the product of answers given after the stimulation interval. Hence response time for the answers given within the stimulation interval was also tested between stimulation and no stimulation.

Case A.M.

In this case, an answer is considered correct whenever the patient stated the correct answer. Failing to respond or giving an incorrect answer is defined as an incorrect answer. Response time was not analyzed in this case because the patient always answered within the stimulation interval.

The difference in proportion of correct answers between stimulation and no stimulations was tested with Chi square analysis on each tested combination of electrodes.

Results

Case B.S.

Stimulation revealed interference with addition and multiplication on several sites. Overall, the epicentre of the significant results is found on the AG ($\alpha<0.05$). No results were found for electrodes situated at the superior parietal cortex.

Mean overall response times for correct answer for the stimulated and non-stimulated trials irrespective of stimulated electrode are shown in table 3a for addition and in 3b for multiplication. For addition and multiplication respectively, response times above 4.15 and 3.99 seconds in the non-stimulated condition and response times above the 10.70 and 7.75 seconds for the stimulated condition were identified as outliers by using the 1,5 IQR criterion. In 2.4 percent of the addition trials (5 out of 205) the patient did not answer and stated he was not able to perform the task. As said, these are considered missing values for this analysis. This did not occur for multiplication. Note that the analyses were performed on the separate combinations and single electrodes.

Table 3a: Mean response times for correct answers for addition

stimulation	Mean (sec)	N	Std. Deviation
no	2.1145	77	0.73296
yes	3.6302	101	2.52058

Table 3b: Mean response times for correct answers for multiplication

stimulation	Mean (sec)	N	Std. Deviation
no	2.3395	19	0.69613
yes	3.2000	26	1.98388

Based on the results of all the described analyses figure 4a and figure 4b were made.

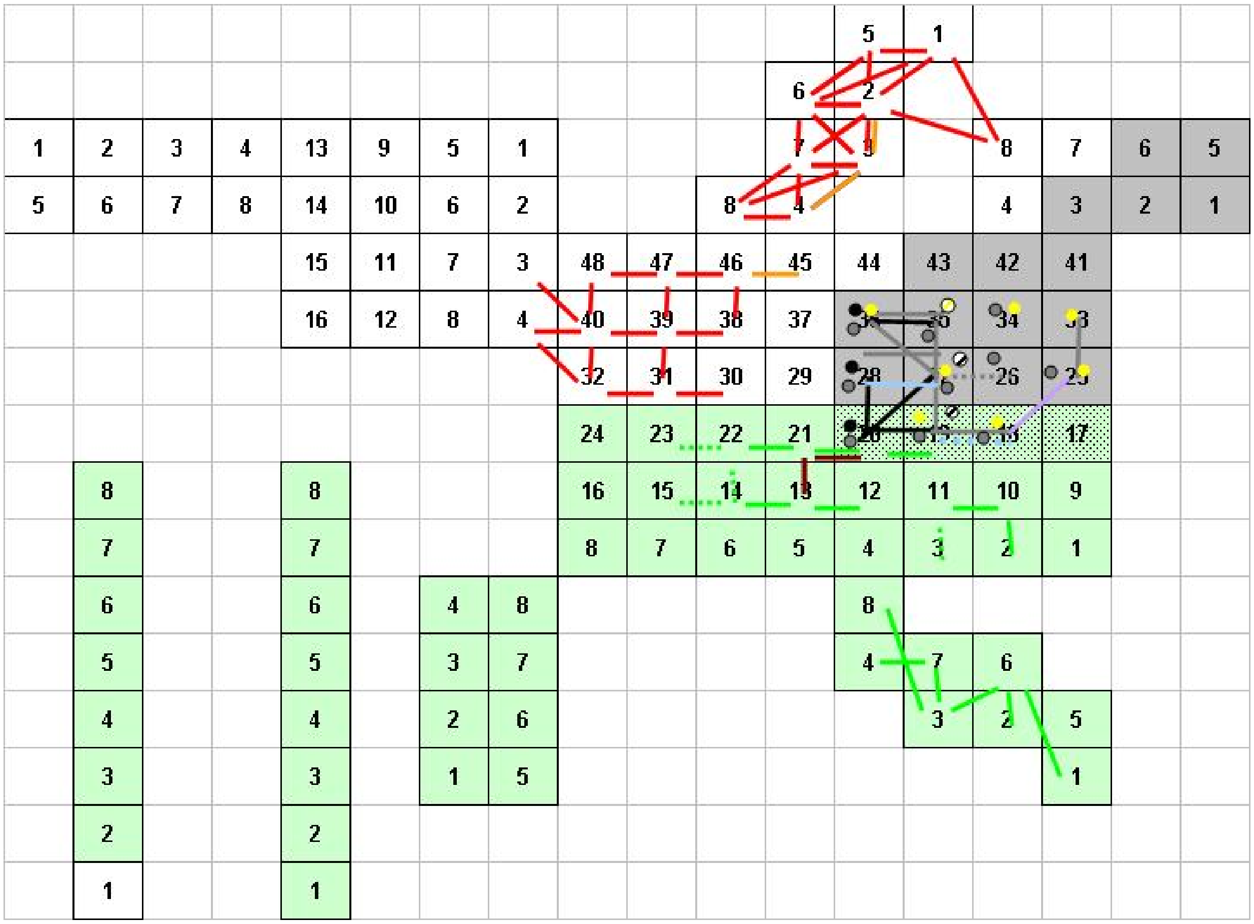


Fig 4a: Results for addition, schematic overview. Numbers in squares correspond to the numbers of the temporary implemented electrodes. Lines represent inter-electrodes results and dots represent results for single electrodes. Note that the results for calculation are based on statistical analyses, whereas the results for language and motor responses are based on clinical observation by another experimenter. A continuous line represents a significant result (α <0.05) and a dotted line or a striped dot represents a trend (0.05<α <0.06).

Caption:

a) Significant chi square results: difference in proportion of correct answers between stimulation and no stimulation for addition

b) Significant chi square results: difference in proportion of 'correct answers in four seconds' between stimulation and no stimulation for addition

● *a) Significant chi square results: difference in proportion of correct answers between stimulation and no stimulation for addition for single electrodes*

● *b) Significant chi square results: difference in proportion of 'correct answers in four seconds' between stimulation and no stimulation for addition for single electrodes*

Significant t-test results: difference in 'time it takes to answer' between stimulation and no stimulation in correct answers for addition

Significant t-test results: difference in 'time it takes to answer' between stimulation and no stimulation in correct answers for addition for single electrodes

Significant t-test results: difference in 'time it takes to answer' between stimulation and no stimulation in 'correct answer in four seconds' for addition

Regions tested for addition

Regions tested for language

Language function: Wernicke's area

Motor functions

Sensorimotor functions

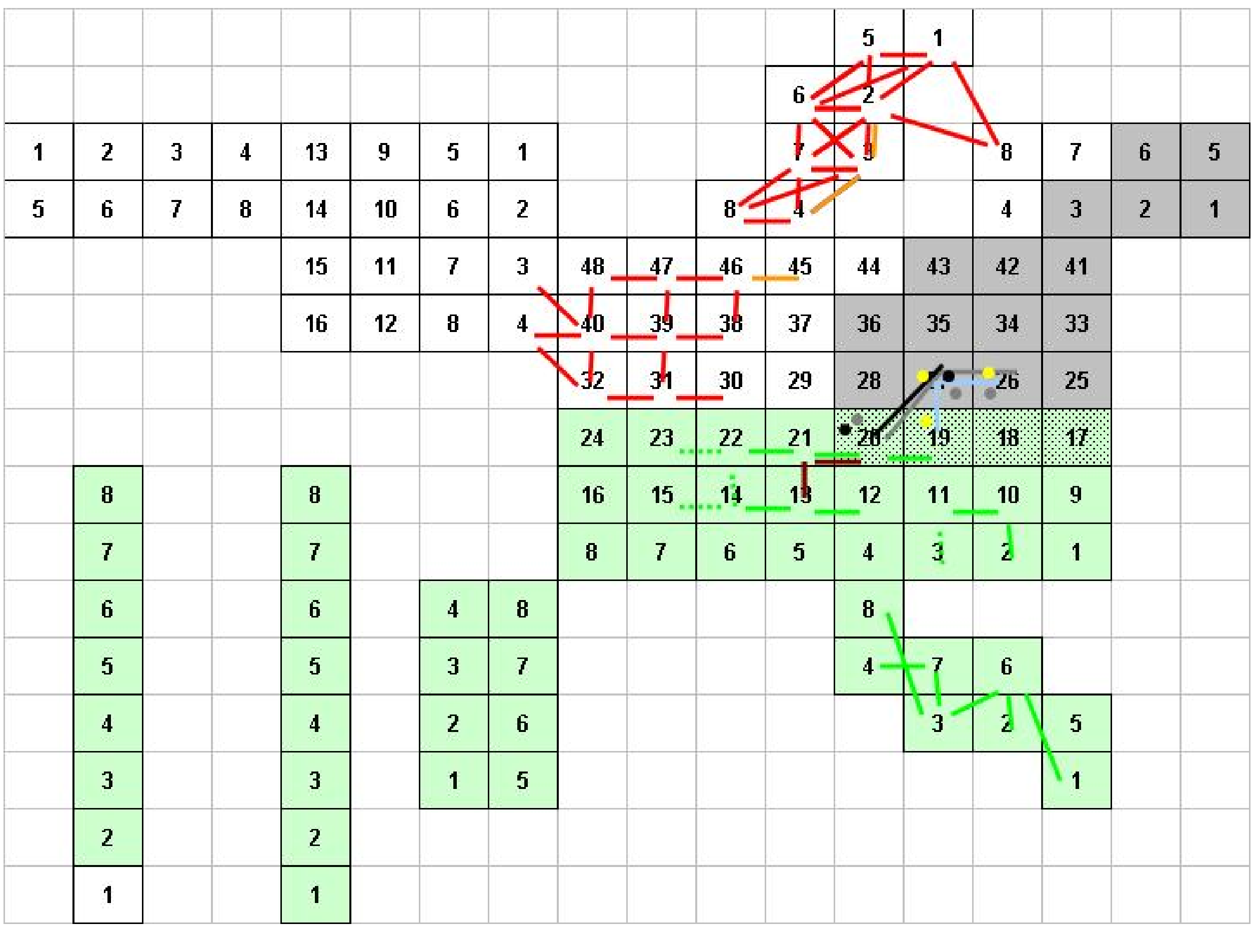


Fig 4b: Results for multiplication, schematic overview. Numbers in squares correspond to the numbers of the temporary implemented electrodes. Lines represent inter-electrodes results and dots represent results for single electrodes. Note that the results for calculation are based on statistical analyses, whereas the results for language and motor responses are based on clinical observation by another experimenter. A continuous line represents a significant result (α <0.05).

Caption:

a) Significant chi square results: difference in proportion of correct answers between stimulation and no stimulation for multiplication

b) Significant chi square results: difference in proportion of 'correct answers in four seconds' between stimulation and no stimulation for multiplication

a) Significant chi square results: difference in proportion of correct answers between stimulation and no stimulation for multiplication for single electrodes

b) Significant chi square results: difference in proportion of 'correct answers in four seconds' between stimulation and no stimulation for multiplication for single electrodes

Significant t-test results: difference in 'time it takes to answer' between stimulation and no stimulation in correct answers for multiplication

Significant t-test results: difference in 'time it takes to answer' between stimulation and no stimulation in correct answers for multiplication for single electrodes

Regions tested for multiplication

Regions tested for language

Language function: Wernicke's area

Motor functions

Sensorimotor functions

For addition, stimulation on combinations of electrodes e20-e19; e20-e27; e20-e28; e35-e36 reveals significant difference in the proportion of correct answers (definition a) between the stimulated and the unstimulated condition (p=0.025; p=0.025; p=0.025; p=0.025). These electrodes cover the more anterior part of the AG (e19, e27, e28, e35), a small part of the SMG (e36) and a part of Wernicke's area (e20). Again, note that the actual location is between the two electrodes. For single electrodes significant results are observed for e28 (p=0.025), situated on the AG, e36 (p=0.025) situated on the SMG and e20 (p<0.01), situated on Wernicke's area. In addition, a trend is revealed at e19 (p=0.057) and e27 (p=0.053), located on the AG.

When the same analysis is done for definition b) of 'correct answer', combinations of electrodes e18-e19 (p=0.018); e19-e27 (p=0.025); e27-e28 (p=0.025); e33-e25 (p=0.025) and e35-e36 (p=0.025) e36-e27 (p=0.046) e35-e27(p=0.025) reveal a significant result and a trend is shown at electrode e26-e27 (p=0.058). This is approximately the same area as for the results in analysis a): the AG (e18, e27, e28, e35), the SMG (36) and Wernicke's area (e20). For single electrodes significant results show at e18(p=0.007), e19(p=0.003), e25 (p=0.002),e26 (p=0.029),e27 (p=0.00),e28 (p=0.002) ,e34(p=0.025),e35 (p=0.002), all situated on the AG, e36(p=0.001) situated at the SMG and e20 (p=0.005), situated at Wernicke's area.

The analysis on response time for correct answers for addition reveals significant results at combination e27-e28 (p=0.041) and a trend on combination e18-e19 (p=0.056), all situated at the AG. For single electrodes, significant results show at electrode e18 (p=0.029), e19 (p=0.005), e25 (p=0.009), e27 (p=0.00), e33 (p=0.045), e34 (p=0.013), all situated on the AG, and e36 (p=0.049), situated on the SMG. A trend is shown on e35 (p=0.053).

Comparing the response time for correct answers within the stimulation interval between stimulation and no stimulation reveals one significant result for addition on combination of electrodes e18-e25 (p=0.031).

For multiplication significant results for the analysis with definition a) of ‘correct answer’ are revealed at the combination of electrodes e20-e27 (p=0.025). This combination is located on the AG. For single electrodes significant results reveal at e27 (p=0.044), located on the AG and on e20 (p=0.025), located on Wernicke’s area.

For definition b) of ‘correct answer’ significant results are revealed at electrode e20-e27 (p=0.025) and e26-e27 (p=0.025), all situated on the AG. Single electrodes reveal significant results at site e27 (p=0.024), e26 (p=0.025), located on the AG and on e20 (p=0.025), located on Wernicke’s area.

The analysis on response time for correct answers for addition reveals significant results at combination e27-e19 (p=0.048) and e26-e27 (p=0.045), all located on the AG. For single electrodes significant results show at e27 (p=0.041), e19 (p=0.048) e26 (p=0.045), all located on the AG as well.

Comparing the response time for correct answers within the stimulation interval between stimulation and no stimulation reveals no significant results for multiplication.

Case A.M.

The functional mapping permitted localisation of sites that disrupt simple exact addition when stimulated. This area is located on the AG. Note that stimulating the more superior part of the AG did not seem to interfere with addition. No results were found for stimulation on the occipital cortex.

Whenever a correct answer was not given in the stimulated condition, the patient stated an incorrect answer in 80 percent (12 out of 15 incorrect answers) of the cases and in 20 percent (3 out of 15) of the cases she expressed her inability to find the correct answer either by saying ‘I don’t know’ or ‘I had to think’.

There were no seizures during testing, but after several stimulations afterdischarge was noticed. These trials are not valid and are defined as missing values because afterdischarge suggests epileptic activity. The next item was postponed until the afterdischarge had ended to prevent interference with calculation.

Chi square for the difference in proportion of correct answers between stimulation and no stimulations revealed a significant disruption for simple exact addition between electrode three and four (p=0.02) and between electrode three and two (p=0.046) (see fig 5.) The interspaces between electrode three and four and electrode two and three are located respectively on the anterior part and the posterior part of the AG. Stimulation of the electrodes on the occipital revealed no interference with simple exact addition.

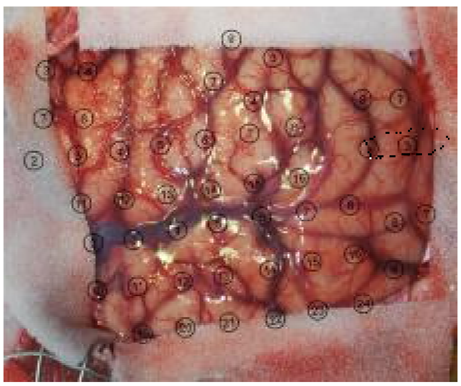


Fig 5: Dotted area represent the area where stimulation interfered with simple exact addition.

Postoperative course

Three weeks after surgery patient A.M. was tested again for simple exact addition tasks. Because the AG was totally spared during resection, no changes in task performance were expected. Indeed, on examination the patient performed 96 percent correctly (24 out of 25), comparable with the 91 percent correct answers in de condition without stimulation during testing (32 out of 35). Patient B.S. was not tested postoperatively for calculation.

Discussion

This study investigated the role of the AG in mental calculation by using cortical stimulation while the patient engaged in simple exact addition and one digit times one digit multiplication. Previous studies suggest that the AG is engaged in the retrieval of verbal calculation facts from memory. This retrieval is thought to be important in tasks such as simple addition and multiplication. It was hypothesized that cortical stimulation on the AG will interfere with these types of sums.

Indeed, in patient B.S. interference of performance in addition and multiplication was found when the AG was stimulated. This interference was found for two separate parameters: the correctness of the answer in definition -a), -b) and the response time for correct sums. Results for addition and multiplication cover roughly the same areas and the difference in the number of significant results between addition and multiplication is probably explained by the difference in number of blocks administered for each type of sums. Stimulation of the superior parietal cortex did not interfere with the ability to produce the correct response and neither with the response time.

In patient A.M., interference of performance was found for simple exact addition tasks on two combinations of electrodes, all situated on the AG, when stimulated. No sites on the occipital lobe yielded significant interference.

The relatively fast answering tendency is a contraindication for quantity manipulation and suggests number fact-based answering. All tasks were solved by A.M. almost immediately after the second digit was presented. In patient B.S. the same was the case for answers in the condition ‘no stimulation’. Moreover, these simple exact addition tasks and multiplication tables are learned early in school and are used in every day life so often that it would be highly unlikely that these tasks should be defined as quantity manipulation. Therefore we assume that the patients solved these tasks by relying on efficient retrieval of mathematical facts from memory.

These results thus correspond well with the proposed function of the AG in the model of Dehaene et al. (2003) as engaged in the efficient retrieval of mathematical facts from memory. Note that the interference occurred when only a small part of the AG was stimulated. This suggests that a small lesion in the AG can introduce interference with calculation. The results are not in line with the findings of van Harskamp et al. (2002) that multiplication is spared while the AG is damaged. It is neither in line with the finding that addition and multiplication are impaired selectively Harskamp & Cipolotti (2001), because the areas where cortical stimulation disturbs addition and multiplication overlap.

The results in this study are the first calculation mapping results that are based on statistical analysis. In this vein, this study is the first to show significant interference due to cortical stimulation on the AG with calculation tasks.

In addition, other mapping studies on calculation do not mention the definition of correct answers as well as about the response time. Although Roux et al. (2003) does notice some answers are given after the stimulation interval, the definition of these occurrences is unclear. Duffau et al. (2002) provides no information about the correct answers produced after the four seconds stimulation interval. According to his study, the patient either gave good answers in the stimulation interval or stated within the interval he did not know the answer because he was instructed so. In spite of this, the procedure of using time related data could be fruitful since the disturbance may not be sufficiently severe to produce incorrect responses, but may slow response time. When comparing the location of significant results for patient B.S. in analysis a) with analysis b) it shows that the results for b) (especially for single electrodes) are somewhat broader. The larger cortical area implicated by analysis b) indicate that defining correctness based on the final answer is not sufficiently sensitive because in that way valuable information is overlooked.

Associated with the results in analysis b) is the finding that in patient B.S. the response time in hundreds of seconds for correct answers was longer when the AG was stimulated compared to no stimulation, for addition and multiplication. Stimulation per se does not induce this slowing, for there is no difference in the time it takes to answer on the superior parietal cortex. An inherent functional characteristic of the AG in this patient thus produced a slowing in answering. When looking at fig 4a and -b, it can be seen that the electrodes at which it takes longer to answer are roughly the same areas as to where analysis b) for single electrodes and addition reveals significant results. It is thus likely that the slowing is explained by the good answers that were produced after the stimulation interval. There are several explanations for the finding: The patient held the answer in working memory because he could not calculate during stimulation or calculating was more difficult and thus took longer, independent of the end of the stimulation. It can be a combination of both. Either way, there is interference. The third possibility is related to language (see below). For the correct answers given inside the stimulation interval, the response time is significantly different between stimulation and no stimulation for one combination of electrodes on the AG for addition. Since this result is based on only four trials (two with and two without stimulation) and since there is only one combination that reveals a significant result and, it could be a spurious finding. This finding should be confirmed with a larger sample.

To my knowledge, this is the first time simple exact 'two digit plus one digit' addition was tested during cortical stimulation over the left angular gyrus. Others have tested multiplication (Whalen et al., 1997), multiplication and subtraction (Duffau et al., 2002) and two digits plus two digit addition (Roux et al., 2003). It has been argued that simple addition is generally solved in a completely automatic fashion and would thus not be suitable for cortical stimulation (Roux et al., 2003). However, interference of the simple exact 'two plus one digit' addition tasks due to stimulation shows that these tasks are in fact suitable for testing during cortical stimulation of the AG. It could be that the automaticity is exactly the process that is being disturbed.

Although the results support the role of AG as defined in the model of Dehaene et al. (2003), these case studies remain inconclusive about a possible smaller involvement in quantity manipulation tasks because no subtraction or other quantity based tasks were tested. Likewise, this study makes no inquiries about a dissociation between the function of the HIPS and the AG, because this first region was not tested and may not be possible to test at all using corticostimulation because of the deep and fairly unreachable anatomical position of a sulcus for electrodes placed on the cortex (see fig 6). Moreover and maybe more detrimental for using cortical stimulation to test the HIPS, the engagement of the HIPS is often bilateral (Dehaene et al, 2003) or even only right-sided (Piazza et al., 2002).

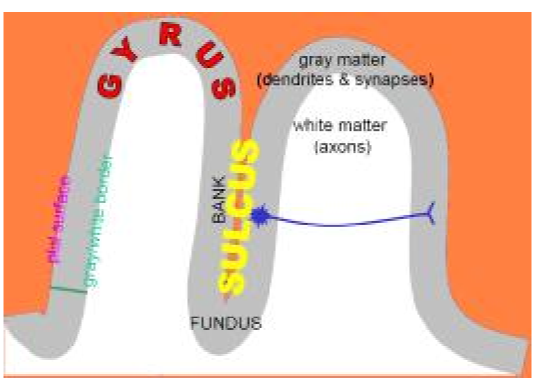


Fig 6: Anatomical position of a sulcus relative to a gyrus.

Insofar the results support the role of, but can not be interpreted as conclusive evidence for the AG as selectively underlying efficient retrieval of mathematical facts from memory.

A limitation of this study is the possible involvement of language. In patient A.M. language was only mapped around the epicenter of the epilepsy due to time restrictions. In patient B.S., as can be seen in fig 4, language was mapped up to the lateral sulcus. The mapping was fairly rough and the results may or may not be significant, but the patient seemed to display Wernicke's aphasia on some of these locations (fig. 4). There is small overlap between these results and the results for addition, and the results on this location might thus be biased due to language functions. It is not known however whether the rest of the AG also is involved in language in this case. There is evidence for a role of the AG in language (Simon et al., 2002; Zago et al., 2001), however this is unlikely to be the sole explanation. First, there is the possibility for speech arrest. Since patient A.M. always stated an answer in the stimulation interval or said could not perform the task, speech arrest can be ruled out in her case. In patient B.S. speech arrest seems unlikely because he did state several answers within the stimulation interval in the epicenter of the significant results. More specifically, the patient provides incorrect answers within the stimulation interval; this contraindicates speech arrest and suggests specific problems with calculation. Second, it would not be surprising that if the essential language area is located in the AG that the patient is unable, on stimulation of the same region, to understand calculations correctly. Nevertheless, the patients did never state that they had not understood the task. They just gave the wrong answer. Moreover, patient A.M. sometimes stated that she was not sure about her answer after she produced it. This indicates a problem with calculation and makes it unlikely that the results are influenced by an understanding problem. However, a subtle naming problem cannot be ruled out.

In the case of patient A.M. another limitation lies in the extent to which the separate sites have been tested. A selection of sites was required because of time restraints. The methodological decision to only test again those sites that seemed to yield responses is precarious because it leads to more statistical power for those sites. So it is not impossible that the other sites would have revealed significant results eventually when submitted to more trials. In patient B.S. the same holds for the multiplication trials. Addition was tested fairly extensively in his case.

In future cortical stimulation studies in which calculation is tested, it is best to test number fact-based as well as quantity manipulation based tasks. It is assumed that multiplication and subtraction could be used for that purpose, although this is not undisputed. Moreover, considering the variety in findings (Harskamp et al., 2005; Harskamp et al., 2002; Delazer &

Benke, 1997; Lee, 2000; Dehaene & Cohen, 1997; Cohen & Dehaene, 2000; Lampl et al., 1994; Pesenti et al., 1994; Lemer et al., 2003) it is clear that this assumption in its own right needs further research. It is also conceivable that individual variation in calculation abilities explain part of the different findings. There are cases known that suffer from highly selective deficits in addition, subtraction or multiplication (Harskamp & Cipolotti, 2001). Therefore, other calculation tasks such as exact and approximate tasks and number comparison should be used in order to be complete, more conclusive about any deficit in calculation tasks and to support or challenges models of the neural substrates of mental calculation.

Up until now only verbal task presentation is used in cortical stimulation studies. In case studies, neuroimaging studies and rTMS studies other modalities have been used for task presentation. In a neuroimaging study of Venkatraman et al. (2005), visual presentation of stimuli is used. Keeping in mind the assumed role of the AG as important in modality specific retrieval of mathematical facts, the presentation in different modalities might not be interchangeable. However, presentation in other modalities does not necessarily exclude verbal retrieval. It is thus ideally that visual as well as verbal presentation are tested in cortical stimulation studies. The same holds for case studies, neuroimaging studies and rTMS studies.

To conclude, in this study, stimulating the AG produces interference with simple exact addition and one digit times one digit multiplication whereas stimulating the superior parietal cortex or the occipital lobe does not. The results of the two cases in this study support the role of the AG as engaged in the efficient retrieval of mathematical facts from memory as postulated by Dehaene et al. (2003). Automaticity in this vein might be exactly the process being disturbed. Also, the results suggest that a small lesion might introduce interference with calculation. This has been the first cortical mapping study on calculation where observations are supported by statistical analysis. Taking response time into account besides correctness of the answers reveals more interference and therefore it can be concluded that stimulation slows answering even for correct answers. Nevertheless, the findings need to be confirmed with larger number of patients in cortical stimulation studies. In addition, the role of possible interference with language function should be considered, a wide variety of calculation tasks including number fact-based versus quantity-manipulation based tasks could be used and the stimuli should be presented in several modalities. Finally, positioning the grid over the AG as well as the SMG and areas closely surrounding the HIPS, may provide the opportunity to gather further information about a possible dissociation between number fact-based and quantity based processes.

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Appendix 1

Table 1: frequencies on the type (addition or multiplication) and number of the sums that were presented with and without stimulation per combination of electrodes for case B.S.

location	location			stimulation		total trials
				no	yes	
Electrodes on the angular gyrus N.B.: When tested in combination with supramarginal gyrus, Wernicke or occipito-temporal junction, the electrodes are marked 'smg', 'w', and 'otj', respectively.						
17 otj	25	type of sum	addition	2	3	5
18	25	type of sum	addition	2	3	5
	17 otj	type of sum	addition	4	6	10
	19	type of sum	addition	4	6	10
	27	type of sum	addition	2	3	5
			multiplication	2	3	5
19	27	type of sum	addition	2	3	5
			multiplication	4	6	10
	20 w	type of sum	addition	2	3	5
20 w	27	type of sum	multiplication	2	3	5
			addition	2	3	5
	28	type of sum	addition	2	3	5
26	25	type of sum	addition	6	9	15
	27	type of sum	addition	4	6	10
			multiplication	2	3	5
	33	type of sum	addition	2	3	5
	34	type of sum	addition	2	3	5
28	27	type of sum	addition	2	3	5
			multiplication	2	3	5
	36 smg	type of sum	addition	2	3	5
33	25	type of sum	addition	2	3	5
34	25	type of sum	addition	2	3	5
	27	type of sum	addition	2	3	5
			multiplication	2	3	5
	33	type of sum	addition	4	6	10
	35	type of sum	addition	2	3	5
	42 smg	type of sum	addition	2	3	5
35	27	type of sum	addition	2	3	5
			multiplication	4	4	8
36 smg	27	type of sum	addition	2	3	5
	35	type of sum	addition	2	3	5
42 smg	41	type of sum	addition	2	3	5
43	35	type of sum	addition	4	6	10
	42 smg	type of sum	addition	2	3	5
Superior parietal cortex						
2	1	type of sum	addition	2	3	5
3	2	type of sum	addition	2	3	5
	4	type of sum	addition	2	3	5
5	1	type of sum	addition	4	6	10
			multiplication	2	3	5
6	2	type of sum	addition	2	3	5
			multiplication	2	3	5
	3	type of sum	addition	2	3	5

Appendix 2

Table 2: Number of the addition sums that were presented with and without stimulation per combination of electrodes for case A.M.

location 1	location 2	stimulation no	stimulation yes	total of trials
Combinations of electrodes on the angular gyrus				
2	3	6	6	12
3	4	6	5	11
8	7	2	2	4
7	6	2	3	5
7	3	2	2	4
8	4	0	0	1
3	8	2	2	4
3	6	2	2	4
2	7	1	2	3
Combinations of electrodes on the occipital lobe				
6	5	2	3	5
1	2	1	3	4
6	2	2	2	4
1	5	1	2	3
2	5	2	3	5
1	6	2	2	4