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Decoding Number Bisection in fMRI

Laboratory report

presented by

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Abstract

Numbers are thought to be represented and processed using a horizontal mental number line, which is oriented from left to right, where small numbers are located on the left and large numbers are located on the right. When tasked to bisect such a mental number line, for example by estimating the mid-number of a given number interval, one can observe consistent underestimation biases in healthy participants, reminiscent of the phenomenon of pseudoneglect in the related visual line bisection task. This number interval bisection bias is modulated by interval magnitude and correlates with different working memory spans. This pilot study investigates the neurological correlates of number interval bisection for small and large intervals using fMRI and how those relate to correlates of verbal and spatial working memory. We found a consistent underestimation bias, which exhibited larger deviations for large intervals for 2 out of 3 participants and interindividual differences in neural activation patterns in brain regions that are typically involved in working memory. While no statistically significant conclusions can be drawn from this pilot, the findings have the potential to guide the overarching study.

1. Introduction

One common theory of how numbers are represented in the mind is the concept of a "mental number line" (Galton, 1880; Dehaene, Bossini & Giroux, 1993). According to this view, numbers are represented along a continuous horizontal mental line, the direction of which is shaped by the reading and writing habits of the culture one grows up with. In western societies, for example, the mental number line is oriented from left to right, where small numbers are located on the left and large numbers are located on the right (Göbel, Shaki & Fischer, 2011; Shaki, Fischer & Petrusic, 2009). This theory is supported by the so-called Spatial-Numerical Association of Response Codes (SNARC) effect, which means that responses to small numbers are faster if they are given using the left body side, while response times are shorter for large numbers if they are associated with the right body side (Dehaene et al., 1993; Hubbard et al., 2005; Priftis et al., 2006).

A task that is commonly used to investigate number-space interactions is the so-called number interval bisection task, which is derived from the visual line bisection task, in which participants are instructed to bisect a horizontal line by marking its midpoint. Similarly, in the bisection of a mental number line, participants are instructed to estimate the mid-number of a given number interval (e.g.: participants are presented with "49" and "81", in which case the correct mid-number would be "65"). In this task, one can observe characteristic biases in both right brain-damaged patients (i.e., neglect) and healthy controls (i.e., pseudoneglect) (Loftus et al., 2009; Rotondaro et al., 2015). Visuospatial neglect is a neurological syndrome that occurs after predominantly right hemisphere brain lesions, and which can affect several modalities. Patients with visuospatial neglect have difficulties in orienting towards the contralesional side and exhibit pathological spatial biases towards the ipsilesional side both at rest and during goal-directed behaviour. For example, during visual line bisection, neglect patients will usually misplace the midpoint to the right (Karnath, 2015; Karnath & Rorden, 2012). In some cases, neglect can also affect mental representations and retrieval of perceptual memories, which is then referred to as representational neglect (Bisiach & Luzzatti, 1978; Beschin et al., 1997).

Zorzi, Priftis and Umiltà (2002) investigated if right-brain damaged patients who were diagnosed with neglect and exhibited a clear associated rightwards bias in the visual line bisection task would show a similar deviation during number interval bisection. In their study, patients heard two numbers in the range of 1 to 25, which defined a number interval of a given length (i.e., 3, 5, 7, 9) and were instructed to verbally estimate the midpoint number without using calculations. Despite showing intact arithmetic skills, neglect patients were reported to exhibit an error bias towards larger numbers as interval size increased. Zorzi et al. concluded that this deficit could be attributed to representational neglect affecting the left side of the mental number line. Further, they claimed that the mental number line has analogous properties to visual lines, even though the mental number line is not represented as a visual line and thus, does not necessarily rely on shared neural mechanisms (Umiltà, Priftis & Zorzi, 2009).

Göbel et al. (2006) and Loftus et al. (2009) found that healthy controls show a slight leftwards bias during number interval bisection, meaning that they tend to underestimate the midpoint number. This was compared to the phenomenon of pseudoneglect, which is observed in healthy participants during the classical line bisection task and characterised by a small systematic shift to the left (Jewell & McCourt, 2000). This bias is attributed to a misallocation of spatial attention along a visual line. Building on this, Longo and Lourenco (2007) showed that pseudoneglect-based biases in the visual line bisection and number interval bisection tasks were positively correlated, which provided further evidence for the hypothesis that number bisection relies on visuospatial attentional mechanisms. They further found number interval bisection biases to be positively correlated with increasing magnitude of the target number that had to be estimated.

More studies have investigated which neural mechanisms may drive number bisection. Hubbard et al. (2005) describe some evidence based on neurophysiological recordings and functional imaging in favour of the spatial attention hypothesis that is also supported by Zorzi et al. (2002) and Umiltà et al. (2009): The areas in the brain that are activated by numerical processing are also implicated in spatial processing to a large extent, such as bilateral intraparietal sulci (IPS) (Kanayet et al., 2018) and posterior parietal cortex (PPC) (Dehaene et al., 2003). In addition to this, Göbel et al. (2006) demonstrated that the disruption of PPC via repetitive transcranial magnetic stimulation (rTMS) induces neglect-like biases in both line and number interval bisection in healthy participants.

Nevertheless, there is also strong evidence against the hypothesis that number interval bisection relies on purely spatial mechanisms. This is based on evidence for the dissociation between perceptual and imaginal space in neglect patients (Guariglia et al., 1993), as well as for the dissociation between performance in visual line and number interval bisection in both healthy controls (Rotondaro et al., 2015) and neglect patients (Pia et al., 2012; Rossetti et al., 2011). This means that there are reports of both controls and patients who show biases in the number interval bisection task, but not in the visual line bisection task and vice versa. Therefore, deficits in number interval bisection and visual line bisection are doubly dissociated (Doricchi et al., 2005). This suggests that the number bisection task is not purely spatially driven, as suggested by Umiltà et al. (2009). While performance in line and number interval bisection tasks may be correlated, Doricchi et al. (2005) showed that severity of neglect is not correlated with systematic deviations in the number interval bisection task. Besides those behavioural data, they also investigated the relation between pathological deviation during number interval bisection and structural brain anatomy. They maintained that activations caused by line bisection are markedly right lateralised and localised in the striate cortex, extrastriate visual cortex, as well as inferior and parietal lobes (Fink et al., 2000), while comparisons of numeric quantities are associated with activations in the bilateral IPS, the left precentral gyrus and, for some tasks, prefrontal areas (Dehaene et al., 2003; Malhotra et al., 2005).

Further, they discovered that only neglect patients who suffered damage to prefrontal areas, which are typically involved in (spatial) working memory, showed biases in numerical comparison and number interval bisection tasks. This suggests that this pathological deviation is more likely due to the inability of building up and maintaining the mental number line within working memory. From this, Doricchi et al. concluded that the mechanisms utilised in estimating the length of a given number interval must be different from those employed in length estimation of visual lines – which stands in direct opposition to the claims by Zorzi et al. (2002).

Further, Aiello et al. (2012) investigated the anatomical correlates of the rightward biases in the visual line and number interval bisection tasks in neglect patients and found those two tasks to be correlated with different neural structures. They concluded that number processing deficits in right-brain damaged patients are likely not due to disruptions of spatial-attentional mechanisms associated with the inferior parietal cortex, but rather of abstract-representational nature, which is associated with the frontal cortex.

Liu et al. (2019) conducted an fMRI study to contrast the neural structures involved in visual line and number interval bisection in healthy participants. Both tasks activated a bilateral parietal-frontal network, which is also implicated in visuospatial attention (Hubbard et al., 2005). Further, they found that the bilateral parietal-frontal areas, left lingual gyrus, precentral gyrus, supplementary motor area (SMA), insula, right calcarine and cerebellum showed higher activations during number interval bisection compared to line bisection and that activations in left SMA and right cerebellum were significantly correlated with performance during the number interval bisection task. This is in line with the findings of Wood et al. (2007), who demonstrated that SMA activation increases with larger interval sizes during number interval bisection, which might be explained by SMA involvement in domain-unspecific sequence processing (Cona & Semenza, 2017). While the role of the cerebellum in number interval bisection has not been fully determined yet, Liu et al. propose that it may facilitate finding the midpoint along a spatially organised (number) line due to its involvement in sensorimotor adaptations and transformations (Martín-Arévalo et al., 2016) and line orientation judgements (Lee et al., 2005). Those results suggest that while number interval and visual line bisection may recruit similar cognitive mechanisms, they are not fully identical.

While those studies established some of the underlying neural structures relevant for numerical processing and tasks like number interval bisection, there is still no consensus on the cognitive underpinnings of the systematic biases in right-brain damaged patients and healthy controls. Besides the hypothesis on systematic spatial working memory impairments grounded in prefrontal lesions as proposed by Doricchi et al. (2005), systematic impairments in verbal working memory (van Dijck et al., 2011) and interindividual differences in working memory and fluency levels (Ranzini et al., 2017) have been proposed.

Van Dijck et al. (2011) described the case of a left-brain damaged patient, who exhibited right-sided neglect for extrapersonal physical and representational space, as well as left-sided neglect for number space. This double dissociation is opposed to what the spatial attention hypothesis by Zorzi et al. (2002) and Umiltà et al. (2009) predicts for the patient's behaviour: According to this theory, the patient's neglect for number space should have followed the direction of neglect for their visual space, however, it was directionally opposed to it. Thorough investigation of the patient's working memory revealed that while their spatial working memory was fully functional, their verbal memory showed low capacity and accuracy problems for the first items of verbal sequences that had to be remembered. Van Dijck et al. followed that the disruption in verbal working memory negatively affected the patient's ability to build up and maintain a sequential verbal representation of ordinal information (= numbers in this case), which manifested as a pathological recency bias towards the "later" items that were to be remembered.

Ranzini et al. (2017) were the first to investigate the relation between interindividual differences in visuospatial attention and other cognitive abilities in a number interval bisection paradigm coupled with an eye pursuit task. While healthy participants engaged in number interval bisection, their visuospatial attention was manipulated by the instruction to follow a horizontally moving dot with their eyes, since attentional orientation and eye movements seem to share neural mechanisms (Casarotti et al., 2012). Interestingly, they found that the underestimation bias during number interval bisection was correlated with verbal working memory span – with higher spans being associated with less biased estimations. Further, only the performance of participants with low verbal working memory spans was influenced by the eye pursuit task: "Low-verbal" participants showed an increased bias towards smaller numbers when their spatial attention was manipulated towards the left. Considering the experimental evidence in favour of the mental number line (e.g.: by Hubbard et al. (2005)), this indicates that this group of participants relied on spatial problem-solving strategies for this task. Conversely, the performance of participants with high verbal fluency levels was not affected by the attentional manipulation, but by the order of presentation of numbers. In case of decreasing order, those participants showed a significantly larger bias towards smaller numbers. This effect of order could be explained by a sort of "recency effect", which shifted their estimation more towards the number that they were last presented with. Further, in line with the findings by Longo & Lourenco (2007), Ranzini et al. found an additive effect between target magnitude and interval length for the underestimation bias: This means that underestimation bias increased with increasing interval lengths and target magnitudes. In an fMRI study, Wood et al. (2007) identified the bisection of large interval ranges to be associated with larger activity in the (pre-)SMA regions, as well as in the intraparietal cortex, which they attributed to increased task difficulty. In summary, while a higher verbal span was indicative of a better performance, a higher verbal fluency was associated with a larger bias.

Overall, it seems plausible that number interval bisection is not a purely spatial task, as was suggested by Umiltà et al. (2009), but that interindividual differences in cognitive abilities, specifically in working memory spans and fluency, may facilitate the employment of different strategies for this task (Ranzini et al., 2017).

Previous studies in the domain of working memory research already established that individual working memory capacity affects brain activity in a non-linear manner: Schneider-Garces et al. (2010) provided first evidence that individuals with lower memory capacity employ higher brain activations in both hemispheres than individuals with higher capacities for tasks that share the same memory load to compensate for the difference in capacity.

Höller-Wallscheid et al. (2017) investigated this further and argued that bilateral activation patterns in the dorsolateral and anterior portions of prefrontal cortex (DLPFC and aPFC) likely act as domain-general support mechanisms compensating for subjectively high task difficulty. They further found bilateral and domain-general activation patterns of the anterior insula and dorsal premotor area (PMd), which they interpreted as reflections of meta-awareness and attention, respectively. At the same time, highly lateralised areas such as the ventrolateral prefrontal cortex (VLPFC), SMA and cerebellum do not recruit their contralateral counterparts when task demands rise, which could be interpreted as an ongoing rehearsal process during memory retention periods (Smith & Jonides, 1999; Ben-Yehudah, Guediche & Fiez, 2007). Combining these findings with the results by Ranzini et al. (2017), it seems likely that in general number interval bisection is facilitated both by spatial and verbal working memory mechanisms, but that participants may either preferentially use verbal or spatial strategies to solve the task or switch between those strategies on a trial-by-trial basis.

Our overarching fMRI study investigates if it is possible to recognise the use of different (working memory) strategies when predicting number bisection deviation from functional brain activity. We aim to train a classifier on the differences in brain activity between working and spatial working memory tasks and then apply this classification to the number interval bisection task.

Due to the time constraints posed by the duration of the laboratory rotation, I conducted a short pilot study for this larger project, in which I investigated the neurological correlates of number interval bisection using fMRI and how those differ between trials involving small (i.e.: interval length <25) and large (i.e.: interval length ≥ 25) number intervals. To this end, data from each participant will be analysed individually.

We hypothesise to find intraindividual differences in

(1) the behavioural data of the number interval bisection task when comparing trials of small (i.e.: <25) and large (i.e.: ≥25) interval sizes. We expect to find a directed effect of interval size on the deviation of the participant's estimated mid-number from the actual mid-number. More specifically, the participants' estimates should show more pronounced deviations from the real mid-number for the large interval condition than for the small interval condition.
(2) the functional data of the number interval bisection task when comparing small and large interval sizes. In particular, we anticipate finding stronger activations in areas that are typically implicated in spatial processes for large interval trials (i.e.: hIPS (Dehaene et al., 2003; Wager & Smith, 2003; Wood et al., 2007)).
(3) the functional data of the working memory task when comparing the verbal to the spatial condition. On the one hand, we expect stronger activations in PMv for verbal trials (Binkofski & Buccino, 2006; Wager & Smith, 2003) and on the other hand, increased activations in hIPS for the spatial condition (Dehaene et al., 2003).

For the purposes of this lab report, only a very small sample size will be considered, which will also serve as a small pilot for the larger overarching project. Further, grounded in the pilot's small sample size, only descriptive statistics will be used for analysing the data.

2. Materials & Methods

2.1. Participants

The overarching study aims to include 30 neurologically healthy participants. Participants will be recruited from the participant pool of the original behavioural study, which included participants recruited from the Section for Neuropsychology's subject database, as well as via the university's mailing list, social media, and bulletin postings within the university clinic of Tübingen. Participants are compensated monetarily (15€ per hour). Both the pilot and the actual study were approved by the ethics committee of the Eberhard Karls Universität Tübingen (Vote 750/2020BO2). For the pilot project that I conducted during my laboratory rotation, we measured 3 healthy participants, who will not be included in the actual study.

Inclusion criteria for the pilot and the actual study are as follows:

- [German native speaker][1]
- Grown up in a country where one reads from left to right
- Right-handedness
- Aged between 18 and 40 years
- No acute presence of or history of neurological/psychiatric diseases or cognitive impairments
- No intake of any centrally active substances/medication (exception: oral contraceptives)
- Normal or corrected-to-normal vision
- No contraindications for MRI, e.g.:
    - metal within the body (e.g.: prosthetics, implants, contraceptive coil, etc.),
    - tattoos,
    - previous surgeries of the brain or heart,
    - claustrophobia,
    - pregnancy, etc.

2.2. Set-Up and Materials

The study is taking place at the 3T Siemens MAGNETOM Prisma MRI Scanner at the University Clinic of Tübingen. Prior to the scanning session, participants receive a short briefing about the study and are screened for fMRI contraindications once again, before giving their written consent. They carry out a short training session on a computer for both tasks before they are being placed in the scanner. To control the experiment, a Windows 10 laptop PC is used to run custom scripts using MATLAB R2015a 64bit (MathWorks) and the Cogent Graphics 2015 toolbox (LON, Wellcome Department of Imaging Neuroscience, London).

Visual stimuli were presented using a projector, which is projecting to a screen that participants were able to see through a mirror mounted on the head coil. The experiment was displayed at a resolution of 1024x768px. Participants were provided with an MR-suitable 5-button response pad which they were instructed to use with their right hand to give their response.

[1] While this was not a requirement for the pilot study, the actual study will only include German native speakers.

2.3. Experimental Procedure

The experiment consisted of two parts: the working memory (WM) task and the number bisection (NB) task.

The WM task comprised a verbal and a spatial condition. Generally, participants were sequentially presented a series of two-digit numbers (4 in the verbal condition, presented for 1500ms each; 6 in the spatial condition, presented for 1000ms each) in the range of 21 to 89. Those numbers were shown in a 4x5 grid, with each number being shown in a different randomised position. In the verbal condition, participants were instructed to remember the values of the shown numbers, while in the spatial condition they were instructed to only remember the position that the numbers were shown in. After fixating on a cross for a variable delay of 15 to 16 seconds, participants were once again presented with a 4x5 containing the same amount of numbers as before (see figure 1). They were now instructed to identify the number whose value (verbal) or position (spatial) had changed compared to the initial presentation. In the verbal condition, all positions were changed as well as the value of a single number. Conversely, all values as well as a single position were changed in the spatial condition to control for potential memory confounds. Participants generated their answer using a 5-button response pad by increasing and decreasing a starting number in steps of 1 and 10, starting from 0. Every block consisted of 16 trials and participants completed two blocks each.

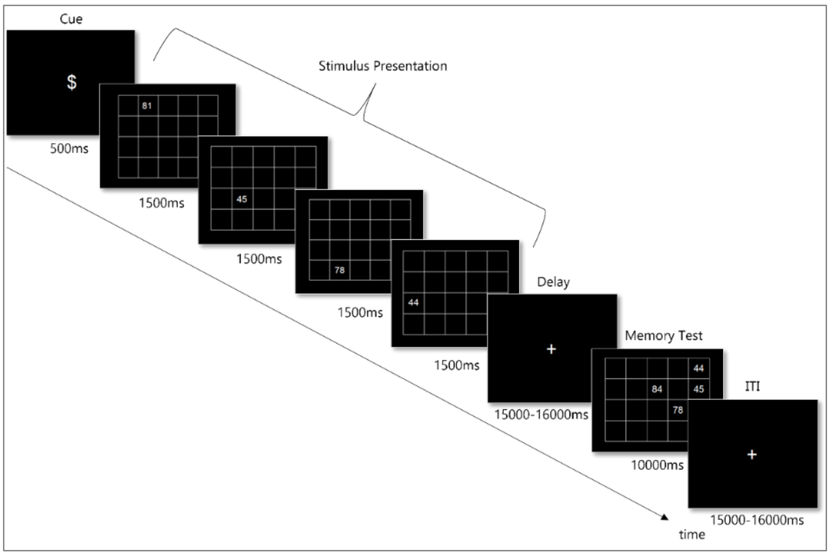


Figure 1: Visualisation of the Working Memory task's verbal condition

In the NB task, participants were sequentially shown two two-digit numbers in the range of 21 to 92 for 1000ms each. Those numbers were shown in a 4x5 grid, with each number being shown in a different randomised position. Afterwards, they were instructed to estimate the mid-number of the given number interval. For example, they would be presented with the numbers “49” and “81” and then give their estimate (see figure 2) – in this case, the correct answer would be “65”.

Participants generated their answer using a 5-button response pad by increasing and decreasing a starting number in steps of 1 and 10. They had a maximum of 7 seconds to enter their estimate but could submit their answer earlier by pressing the middle button of the response pad. The starting number was randomised to either the lower or upper number describing the number interval that was presented prior to the estimation. After the answer was submitted, an intertrial interval followed, in which a fixation cross was shown for a randomised duration of 15 to 16 seconds. Every block consisted of 20 trials and participants completed 2 to 3 blocks[2].

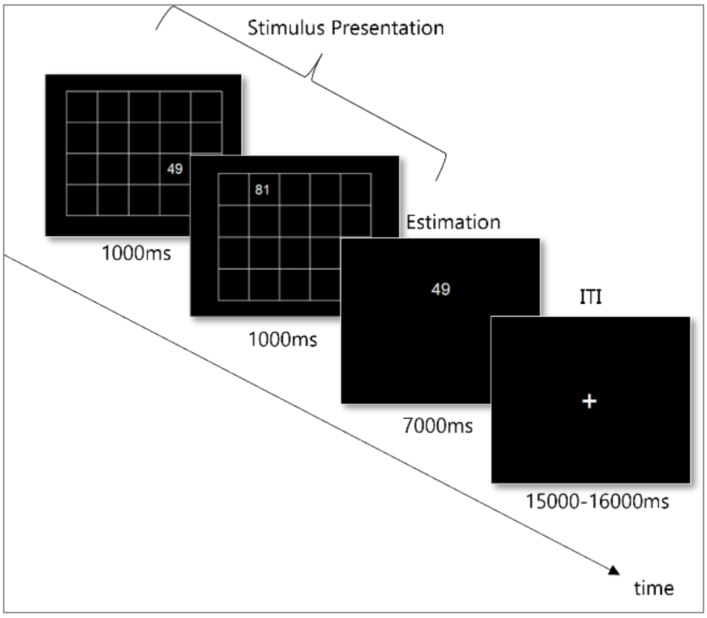


Figure 2: Visualisation of the Number Bisection task

Our tasks differed visually from typical set-ups of number interval bisection and working memory tasks, since we decided to display the numbers to bisect in a 4x5 grid at randomised spatial locations and to use two-digit numbers for the verbal and spatial working memory tasks, rather than strings of letters and spatially arranged dots, respectively. We chose this set-up to make the two tasks as similar to each other on a visual level as possible. This is crucial in order to reliably identify the neural correlates of verbal and spatial problem-solving strategies in different tasks, while eliminating confounding activations arising from differences in visual stimulation.

[2] Participants 1 and 2 only completed two blocks due to exhaustion and time constraints, while participant 3 completed three blocks.

2.4. Data Acquisition & Pre-processing

Data acquisition was performed using a 3 Tesla Siemens MAGNETOM Prisma MRI Scanner with a 20-channel head coil (Siemens Healthcare GmbH, Erlangen, Germany) at the Division of Biomedical Magnetic Resonance, Department of Radiology at the University Clinic of Tübingen. First, a high-resolution T1-weighted anatomical scan was acquired for every participant using an MPRAGE sequence (176 slices, TR = 2300ms, TE = 2.96ms, slice thickness = 1 mm, voxel size = 1 x 1 x 1 mm^3, flip angle (FA) = 8 deg). Afterwards, whole-brain echo-planar images (EPI) were acquired using an interleaved scanning design (48 slices, TR = 2000ms, TE = 35ms, slice thickness = 3 mm, voxel size = 3 x 3 x 3 mm^3, FA = 75 deg, FoV read = 1344mm).

The functional data were pre-processed using MATLAB R2018a 64bit (MathWorks) and the SPM12 toolbox (Wellcome Department of Cognitive Neurology, London). For pre-processing, the functional images from all blocks were first realigned to the first scan of the first block of the respective task as a reference to correct for head movements during the scan. The T1 anatomical image was co-registered to serve as a reference image and all functional images were aligned to the mean anatomical image based on the co-registration. Then, the anatomical image was normalised in MNI (Montreal Neurological Institute) space and the resulting normalisation parameters were used as a deformation field to spatially normalise the functional images for both tasks. A 6 x 6 x 6 mm^3 full-width at half-maximum Gaussian filter was used to smooth the functional images, before applying a 128Hz high-pass filter.

The behavioural data were pre-processed using R version 4.1.1 (R Core Team, 2021) and tidyverse version 1.3.1 (Wickham et al., 2019). For the NB task, trials were excluded in which answers were given that were outside of the number interval. For the WM task, no trials were excluded. However, due to a technical error during data acquisition, participant 1's data could not be analysed and were therefore discarded.

2.5. Data Analysis

Data analysis of the behavioural data was performed using R version 4.1.1 (R Core Team, 2021) and tidyverse version 1.3.1 (Wickham et al., 2019). Summary statistics were computed on the level of conditions and participants. We computed the mean response accuracy for both tasks. For the NB task, the mean deviation of the given estimate from the true mid-number was calculated additionally.

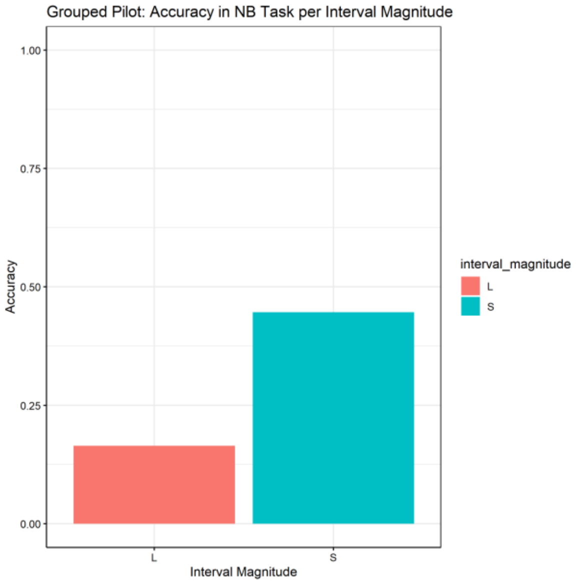
The functional data were analysed using MATLAB R2018a 64bit (MathWorks) and the SPM12 (Wellcome Department of Cognitive Neurology, London) and NERT4SPM (Lindner & Budziszewski) toolboxes. The data was corrected for multiple comparisons using FWE correction (p = 0.05).

Based on the previous studies in the field of number cognition and working memory research, we selected 2 regions of interest (ROIs) for the data analysis, namely the horizontal segment of the right intraparietal sulcus (hIPS) and left ventral premotor cortex (PMv) (see appendix table 01 for MNI coordinates). For those ROIs, we examined the neural activity's event-related time courses, as well as the beta weights on a condition level for each participant.

3. Results

3.1. Behavioural Results

The number interval bisection task had an overall accuracy level of 0.28, with 0.16 for large intervals and 0.45 for small interval sizes (see figure 3a). Participant 1 showed higher accuracy for trials of large interval magnitude (0.23) than for those of small magnitude (0.15). For participants 2 and 3, the opposite trend was found, as they exhibited a larger proportion of correct answers for small interval trials (0.47 and 0.58, respectively) than for large interval trials (0.04 and 0.21) (see figure 3b). It is noteworthy that participant 2 showed the lowest overall accuracy for the large interval condition at a level of only 0.04 correct estimates (see also appendix: table 02).



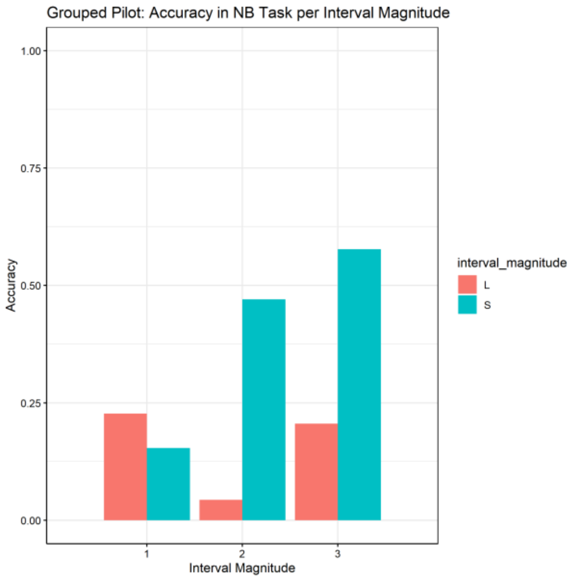


Figure 3: Response accuracy in the number bisection task
(small intervals in blue, large intervals in red)
3a (left): Aggregated accuracy on the condition level (small vs. large intervals)
3b (right): Accuracy on the participant level

All mean deviations were negative. The large and small interval conditions exhibited different mean deviations on the condition level. While the mean deviation from the true mid-number was -1.747 for large intervals, it was -1.179 for small intervals on average (see figure 4a). We found both intra- and interindividual differences while comparing deviations of the participants' estimates from the actual mid-number when taking the two interval magnitudes into account: Similar to what was already observed for accuracy, while for participant 1, the deviation decreased with increasing interval magnitude, the opposite trend was found for participants 2 and 3 (see figure 4b).

The largest overall deviation from the actual mid-number was found for participant 2 in the large interval condition (μ(dev) = -2.83), while participant 3 exhibited the smallest overall mean deviation at -0.54 in the small interval condition (see also appendix: table 03).

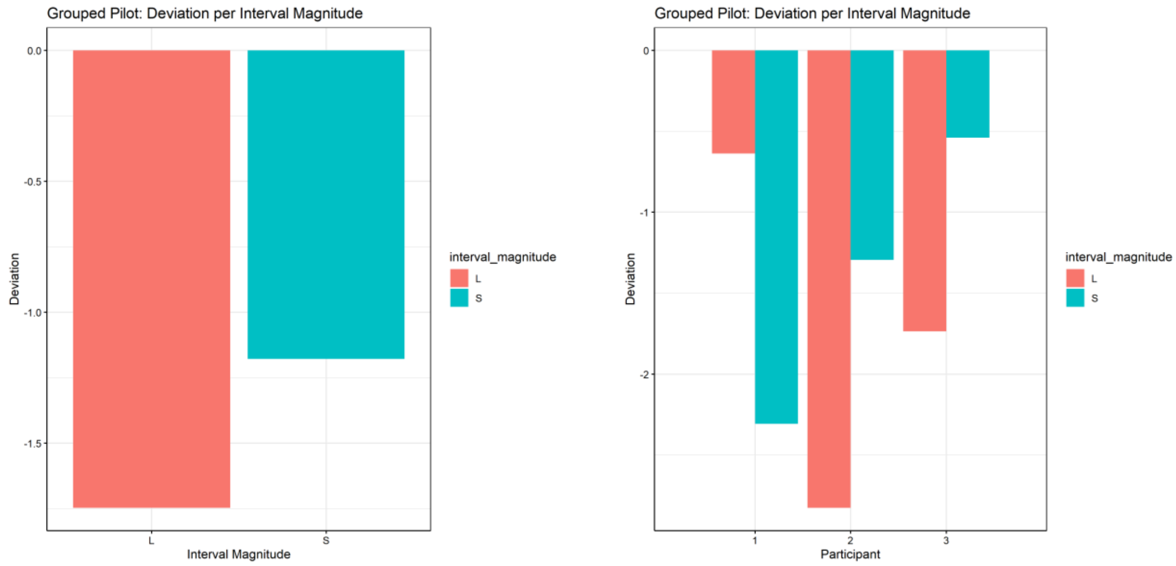


Figure 4: Mean response deviation from true mid-number in the number bisection task (small intervals in blue, large intervals in red)
4a (left): Aggregated mean deviation on the condition level (small vs. large intervals)
4b (right): Mean deviation on the participant level

The working memory task had an overall accuracy of 0.669, with 0.589 for the spatial condition and 0.75 for the verbal condition (see figure 5a). All participants exhibited a response accuracy of 0.75 for the verbal condition. For the spatial condition, accuracy was at 0.5625 for participants 2 and 3 and at a level of 0.625 for participant 1 (see figure 5b and appendix: table 04).

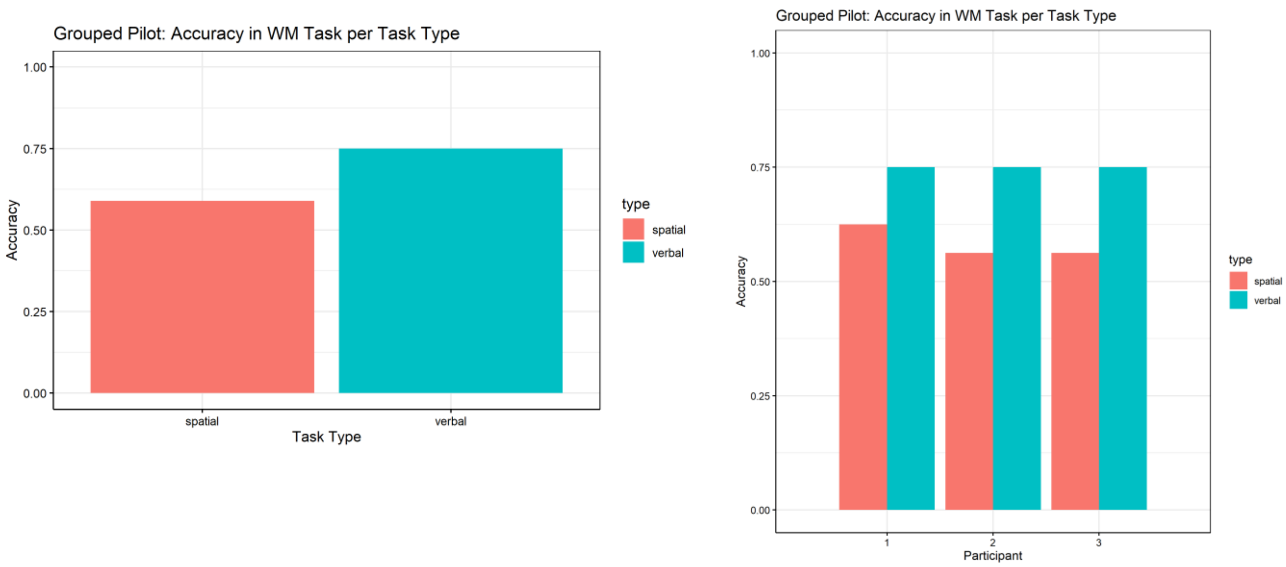


Figure 5: Mean response accuracy in the working memory task (verbal condition in blue, spatial condition in red)
5a (left): Aggregated mean accuracy on the condition level (verbal vs. spatial)
5b (right): Aggregated mean accuracy on the participant level

3.2. fMRI Results

To get a first overview over the data, we visually inspected the whole-brain activation patterns for both tasks individually on the participant level. We differentiated between 2 phases for the NB task (stimulus presentation vs response) and 3 phases for the WM task (stimulus presentation vs delay vs response). However, we only considered the stimulus presentation phase for the NB task and the delay phase for the WM task for the analyses.

In the NB data, the stimulus presentation phase was characterised by activations that primarily occurred in occipital (incl. left lingual gyrus, left fusiform gyrus, bilateral superior occipital gyrus) and temporal regions (incl. bilateral middle and superior temporal gyri), and some activation in the regions surrounding the central sulcus (incl. left post- and precentral gyrus). In contrast to that, we mainly found activations in parietal (incl. bilateral superior parietal lobule and supramarginal gyri) and frontal regions (incl. bilateral middle frontal gyri and right superior frontal gyrus) during the response phase. We also found large activation patterns in regions surrounding the central gyrus again, as well as in SMA. Generally, the activation blobs were larger for the large interval condition than for the small interval condition for both phases (see figure 6).

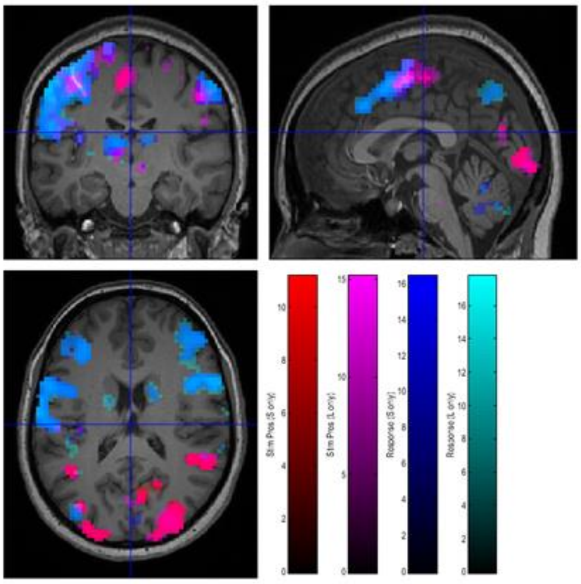
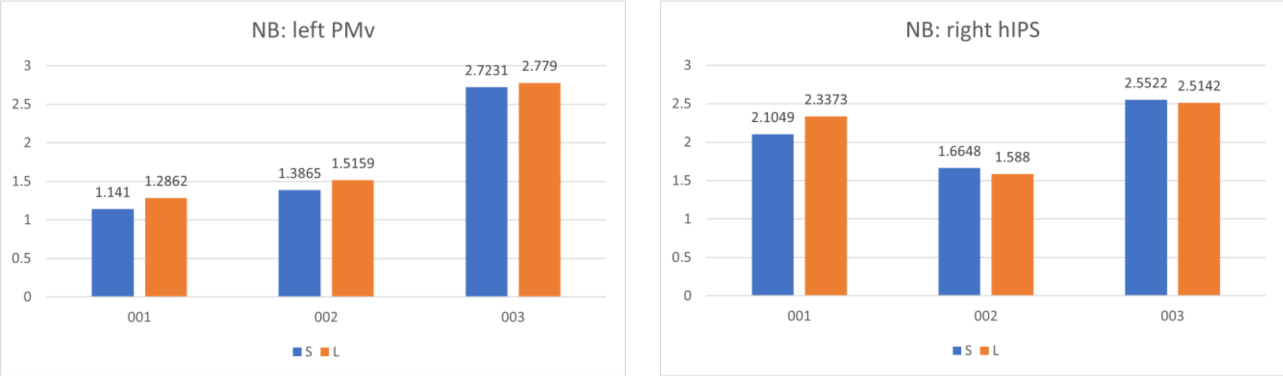


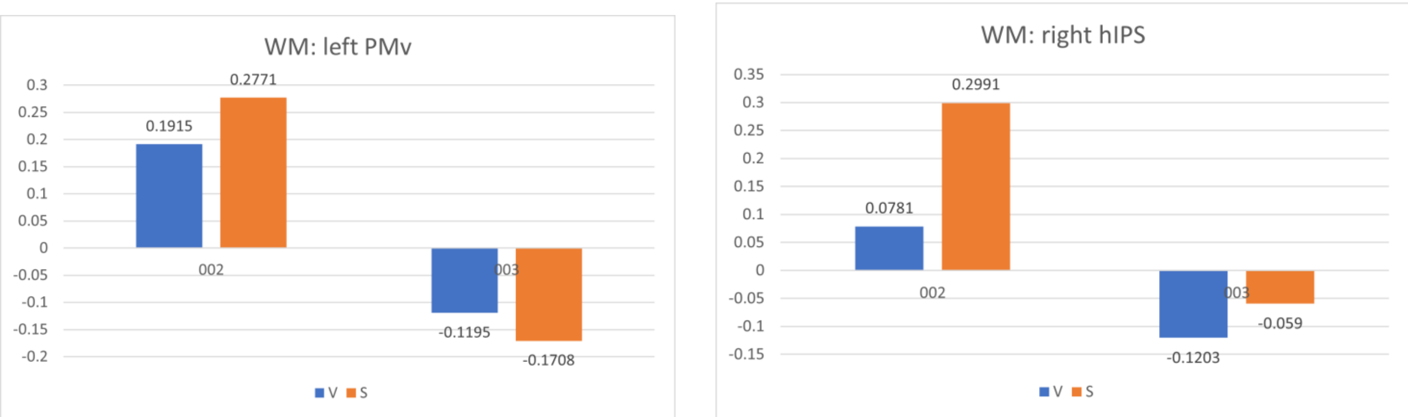
Figure 6: Whole-brain activation patterns of participant 2 in the number bisection task
Red: Stimulus presentation phase for small interval condition
Pink: Stimulus presentation phase for large interval condition
Blue: Response phase for small interval condition
Turquoise: Response phase for large interval condition

We then investigated the beta weights for our two ROIs on the participant level (see appendix: table 05 for all values). We found a consistent trend of higher beta values for the large interval condition than for the small interval condition in left PMv (see figure 7a). In right hIPS, however, only participant 1 showed the same trend, while participants 2 and 3 exhibited the reverse pattern (see figure 7b).



<u>Figure 7:</u> Beta weights for the stimulus presentation phase of the number bisection task on the participant level (small intervals in blue, large intervals in orange)
<u>7a</u> (left): Beta weights for left PMv
<u>7b</u> (right): Beta weights for right hIPS

When looking at the beta weights of the WM data (see appendix: table 06 for all values), it is striking that participant 2 showed activations within their ROIs, while participant 3 exhibited deactivations. Further, participant 2 showed a consistent trend of larger activations (as approximated by the beta weights) for the spatial condition than for the verbal condition across both ROIs. Participant 3, however, showed two distinct patterns: Within the left PMv, they exhibited less deactivation for the verbal condition, while we found lower deactivations for the spatial condition within the right hIPS (cf. figures 8a & 8b). Taken together, the two participants showed consistent trends of activation patterns within right hIPS, but not in left PMv.



<u>Figure 8:</u> Beta weights for delay phase of the working memory task on the participant level (verbal condition in blue, spatial condition in orange)
<u>8a</u> (left): Beta weights for the left PMv
<u>8b</u> (right): Beta weights for the right hIPS

Lastly, we visually examined the event-related time courses of the neural activity. For the NB task, we found activity (as approximated by percent signal change) for the large interval condition to be higher than for the small interval condition on average in left PMv across participants (see appendix: figure 01). In right hIPS the effects were not as consistent across the time course, the large interval condition's curve still exhibited the largest global peak. In the WM task, the time courses of the two participants differ substantially. Participant 3's curves of the verbal and spatial conditions reach different levels of activity, show very robust effects as evidenced by their narrow standard errors and do not cross over each other during the entirety of the trial length (see figure 9a). In case of participant 2, the curves cross over multiple times and possess large standard errors that partially overlap with the other curves (see figure 9b):

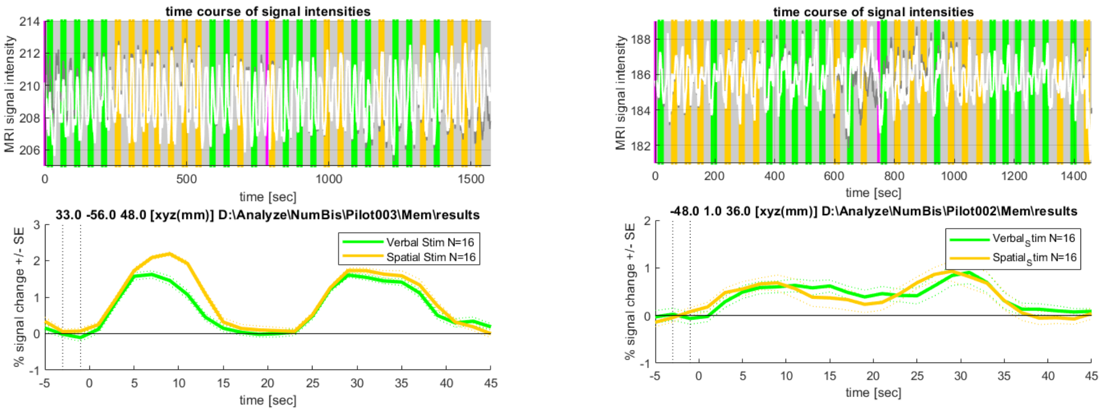


Figure 9: Exemplary neural event-related time courses for the working memory task during the delay phase (verbal condition in green, spatial condition in orange)
9a (left): Participant 3's average time courses for right hIPS
9b (right): Participant 2's average time courses for left PMv

4. Discussion

The present study investigated the neural correlates of number interval bisection using fMRI and how those differed between small and large number intervals in two regions of interest, namely left PMv and right hIPS, which are typically involved in verbal and spatial working memory, respectively.

We found robust negative deviations of the participants' estimates from the real mid-number in all participants across conditions. Therefore, we were able to replicate the "pseudoneglect"-like underestimation bias that one would expect from healthy participants in such a number interval bisection task (e.g.: Göbel et al., 2006; Loftus et al. 2009; Longo & Lourenco, 2007).

Further, we found a relatively low mean response accuracy during the number interval bisection task, which we expected, as the task was designed to be hard to solve in the provided time limit. This was crucial for the data analysis, as we were primarily interested in the errors of the participants. Still, two participants had percentages of about 50% correct answers (0.47 and 0.58, respectively) for the small interval condition, with a much lower percentage of correct answers for large intervals with accuracy rates as low as 0.04 in one participant. This suggests that the difficulty between the two conditions may not have been matched[3].

However, contrary to what we expected based on Ranzini et al. (2017)'s findings, our participants' estimate did not consistently deviate more from the real mid-number for the large interval condition. While two of our three participants showed this effect, the effect was reversed in another participant, who exhibited more pronounced deviations for the small interval conditions. There are a number of possible reasons for this, such as differences in our participants' native languages and the associated (lack of the) numerical inversion effect in two-digit number words (Klein et al., 2013; Savelkouls, Williams & Barth, 2020)[4] or differences in arithmetic skill levels (Amalric and Dehaene, 2018; Ischebeck et al., 2006; Wood et al., 2007).

All our participants showed stronger activations for large compared to small intervals in the left PMv. Though we did not formalise any hypotheses about the activation patterns in PMv for the number bisection task, this finding is in line with the study by Wood et al. (2007), who found that bisection of large number intervals coincided with increased activation in the bilateral intraparietal and (extra-)striate cortices, as well as in SMA and premotor cortex.

[3] While we found overall higher response accuracy during the working memory task, we also detected an effect of the condition on the accuracy – albeit less pronounced than during the number interval bisection task. Here, participants consistently showed higher response accuracy for the verbal condition. For this reason, it seems likely that the two conditions of this task were not matched in difficulty either.

[4] Participant 1 is a native speaker of Catalan and reported to have solved the task (mentally) in Catalan as well, while participants 2 and 3 are German native speakers. German is characterised by a numerical inversion effect, which means that in two-digit number words the decade and units are inverted (e.g.: 41 is "einundvierzig" in German, which literally translates to "one-and-fourty"), while this is not the case in Catalan.

Based on this study, as well as the studies by Dehaene et al. (2003) and Wager & Smith (2003), we expected to find stronger activations for large intervals in hIPS. However, when looking at the beta weights of neural activations, we found the opposite effect for two of our three participants.

Interestingly, the investigation of the neural event-related time-courses revealed that the global peak of percent signal change occurred for the large interval condition, which is in line with our initial hypotheses again. While we expected to find a consistent effect for both the time-courses and the beta weights, it is not uncommon to see dissociations when comparing the two, as one represents a single-valued summary statistics, while the other represents changing values over a time series.

The most unexpected finding we encountered during the pilot study were the deactivation patterns that participant 3 exhibited during the delay phase of the working memory task. Normally, one would expect to find activation patterns in areas related to working memory during the delay phase of such a task – even if subjective task difficulty is low (see e.g.: Höller-Wallscheid et al., 2017). What also speaks against the theory that the working memory task was significantly too simple for the participant are their accuracy levels, which are average when comparing them to the other participants. Interestingly, however, participant 3 also exhibited the greatest difference in percent signal change when comparing the neural event-related time-courses across conditions. While we cannot explain these findings, our working hypothesis for the time being is that this participant may have used a different encoding strategy for the items that they wanted to keep in their working memory, such that an ongoing mental rehearsal process during the delay period would have been redundant.

When we subsequently inspected the data in an exploratory manner, we found a potential anti-correlation between the behavioural data and the functional brain activity in the number interval bisection task: Our participants exhibited reversed condition effects when comparing their estimate's deviation from the real mid-number (c.f. figure 4b) to the beta weights (c.f. figure 7b). Participant 1 showed larger deviations for small number intervals and increased beta weights for large intervals in hIPS, while this pattern was reversed for participants 2 and 3. Due to time constraints, we were not able to analyse this relation any further, but it seems as if brain activation patterns may be able to predict behavioural biases during number interval bisection.

To summarise, our results were able to replicate the consistent underestimation bias that is typically shown by healthy controls during number interval bisection. Further, we detected more pronounced deviations of two of our three participants' estimates from the real mid-number for large interval sizes compared to small intervals. we did not meet our initial hypotheses of finding increased neural activity in 1) areas involved in spatial working memory, such as hIPS, for large intervals during the number interval bisection task and 2) hIPS for the spatial condition and PMv for the verbal condition of the working memory task.

However, our findings can be interpreted as interindividual differences between those patterns of neural activity, which seems promising considering the aim of the overarching fMRI study, which intends to train machine learning classifier to predict deviation behaviour during number bisection from differences in working memory-based brain activity.

Nevertheless, it must be acknowledged that the present pilot is restricted by a number of limitations.

Firstly, due to our very small sample size, the statistical power of analyses is low, which is why opted to employ a purely descriptive approach to statistics. So, one must keep in mind that our findings may not be representative of a larger population.

Secondly, due to limitations in time, there were several aspects we could not analyse or account for during the present study. For one, we were unable to analyse response times due to shortcomings in the current implementation of the experiment, which we only realised after completing data collection. When adjusting the experiment for actual study, however, RTs will be taken into account to ensure more accurate analyses. Another large limitation is that we only took two ROIs, namely left PMv and right hIPS, into account for our analyses. Typically, comparable fMRI studies analyse a greater number of ROIs. This seems especially necessary/reasonable when researching higher cognitive functions, such as working memory, that are known to be grounded in spatially extended functional brain networks that can extend over both hemispheres (Geier, Garver & Luna, 2007; Pessoa et al., 2002; Höller-Wallscheid et al., 2017). However, even though our hypotheses were only partially met in this pilot, we are still confident in our initial choice of ROIs and thus, will keep them for our future analyses. For the larger overarching study, we plan to include more ROIs in our analyses, such as the right superior parietal lobule (SPL), SMA, left angular gyrus and the left hemispheric counterpart to hIPS, as well as left inferior frontal gyrus (IFG) and superior temporal gyrus (STG), as the functions of those areas is already well established in the literature on numerical cognition and working memory (e.g.: for reviews see Dehaene et al., 2003; Wager & Smith, 2003; Zacks, 2008).

Thirdly, we did not control for differences in subjective working memory load and associated differences in subjective task difficulty, which may have distorted our results. For example, participant 2 told us that they found the spatial working memory task to be very challenging, while participant 3 described this task as "fun and easy". One possibility to control for such interpersonal differences would be to adopt a similar approach to the one by Höller-Wallscheid et al. (2017), who determined their participants' working memory spans prior in a purely behavioural task prior to their scanning sessions, such that they could adjust working memory loads to ensure comparable levels of subjective difficulty.

One major drawback that arises from the combination of our very limited number of ROIs and the lack of control for differences in subjective task difficulty is that it is possible that the differences in brain activations that we detected may have been caused by differences in (subjective) difficulty rather than a true effect of interval size. For example, Höller-Wallscheid et al. (2017) have shown that when (subjective) task difficulty increases, cross-hemispheric counterparts of prefrontal brain structures that are involved in working memory are recruited to cope with high cognitive demands.

While we did not investigate if bilateral recruitment of cross-hemispheric structures occurred, we found slightly larger activation blobs for the large interval condition than for the small interval condition (cf. figure 6), it is possible that this spatially more extended activation pattern could be attributed to higher cognitive demands.

Fourthly, the mode of answering may not have been optimal for the present task and thus, might be subjected to change for the actual study. In the present pilot, participants were presented with visual stimuli and also had to generate a visual stimulus for their response via button press. In many other studies employing the number interval bisection task, either the presentation of stimuli or the participants' response or both occurred verbally (see e.g.: Priftis et al., 2006; Ranzini et al., 2017). Our choice to move both stimulus presentation and the participants' response into the visual domain may have affected our results as it seems possible that this way, participants may have processed numbers in a purely visual way rather than engaging with their associated semantics (Dehaene, 1992; Dehaene et al., 1993 & 2003). Thus, it may be interesting to see if we would be able to find the same effects if we were to do another short pilot study, in which participants had to give their answers verbally, for example.

After concluding this pilot study, many open questions still remain to be answered in the upcoming actual study, as well as potential future studies. While this pilot mostly served as a "sanity check" to see if the data we collected would be consistent with the literature from the field, the main aim of the actual study will be to investigate if working memory strategy usage can be predicted from functional brain activity using a decoding algorithm. To conclude, this pilot was able to partially replicate the effects commonly described in the literature in the field of numerical cognition and working memory research. We identified some weak points of the current study design, most notably a too low number of ROIs and the lack of control for subjective task difficulty, which will be adjusted for the upcoming study. Despite the pilot's shortcomings, we already found a potential relation between behavioural biases and brain activation patterns, which seems promising in light of the decoding approach that the upcoming study will take.

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Appendix

Supplementary Tables

Table 01: MNI coordinates

Area	Starting MNI coordinates			Participant 001			Participant 002			Participant 003		
	x	y	z	x	y	z	x	y	z	x	y	z
Right hIPS	36	-52	44	30	-57	51	27	-50	42	33	-56	48
Left PMv	-43	2	37	-36	6	24	-48	1	36	-39	1	33

Table 02: Number Bisection Accuracy – Participant Level

Participant	Interval Size	Hits/Misses	Accuracy
001	Small	2/11	0.154
	Large	5/17	0.227
002	Small	8/9	0.471
	Large	1/22	0.043
003	Small	15/11	0.577
	Large	7/27	0.206

Table 03: Number Bisection Mean Deviations – Participant Level

Participant	Interval Size	Mean Deviation
001	Small	-2.30769231
	Large	-0.63636364
002	Small	-1.29411765
	Large	-2.82608696
003	Small	-0.53846154
	Large	-1.73529412

Table 04: Working Memory Accuracy – Participant Level

Participant	Condition	Hits/Misses	Accuracy
001	Verbal	18/6	0.7500
	Spatial	15/9	0.6250
002	Verbal	12/4	0.7500
	Spatial	9/7	0.5625
003	Verbal	12/4	0.7500
	Spatial	9/7	0.5625

Table 05: Betas weights for the Number Bisection Task (right hIPS & left PMv)

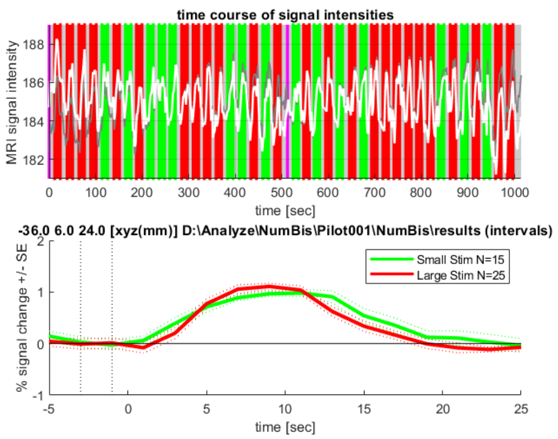
Participant	ROI	Stim Pres. – Small Intervals	Response – Small Intervals	Stim Pres. – Large Intervals	Response – Large Intervals
001	hIPS	2,1049	0,8733	2,3373	0,8687
	PMv	1,141	0,9843	1,2862	1,1156
002	hIPS	1,6648	0,3249	1,588	0,281
	PMv	1,3865	0,9925	1,5159	0,9901
003	hIPS	2,5522	0,3875	2,5142	0,488
	PMv	2,7231	0,3367	2,779	0,4012

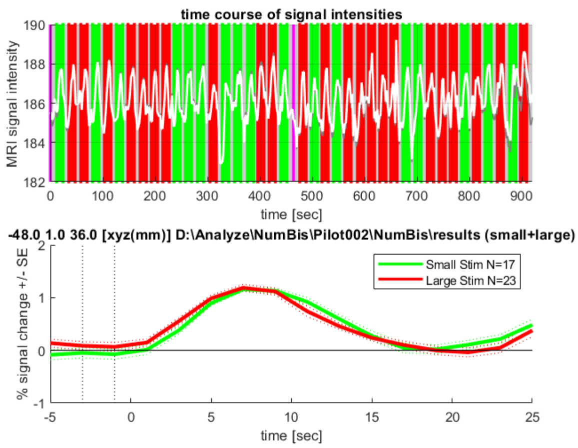
Table 06: Beta weights for the Working Memory Task (right hIPS & left PMv)

Participant	ROI	Stim. - Verbal	Delay - V	Resp. - V	Stim. - S	Delay– S	Resp. – S
002	hIPS	0.8507	0.0781	0.9549	0.8377	0.2991	0.8109
	PMv	0.5670	0.1915	0.8708	0.6441	0.2771	0.7284
003	hIPS	1.7201	-0.1203	1.4314	2.1504	-0.0590	1.6209
	PMv	1.7681	-0.1195	1.2872	1.8345	-0.1708	1.3622

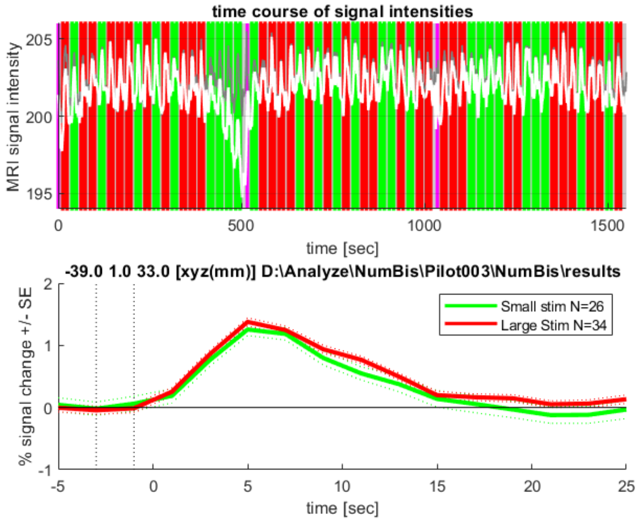
Supplementary Figures

Figure 01: Event-related time courses of the neural activity in left PMv in the Number Bisection Task across participants





Left: Participant 1
Right: Participant 2
Bottom: Participant 3


time course of signal intensities
MRI signal intensity
205
200
195
0
500
1000
1500
time [sec]
-39.0 1.0 33.0 [xyz(mm)] D:\Analyze\NumBis\Pilot003\NumBis\results
% signal change +/- SE
2
1
0
-1
-5
0
5
10
15
20
25
time [sec]
Small stim N=26
Large Stim N=34