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Bidirectional modulation of numerical magnitude

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Running Title: Control of Number Allocation

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ABSTRACT

Numerical cognition is critical for modern life; however, the precise neural mechanisms underpinning numerical magnitude allocation in humans remain obscure. Based upon previous reports demonstrating the close behavioural and neuro-anatomical relationship between number allocation and spatial attention, we hypothesised that these systems would be subject to similar control mechanisms, namely dynamic interhemispheric competition. We employed a physiological paradigm, combining visual and vestibular stimulation, to induce interhemispheric conflict and subsequent unihemispheric inhibition, as confirmed by transcranial direct current stimulation (tDCS). This allowed us to demonstrate the first systematic bidirectional modulation of numerical magnitude towards either higher or lower numbers, independently of either eye movements or spatial attention mediated biases. We incorporated both our findings and those from the most widely accepted theoretical framework for numerical cognition, to present a novel unifying computational model which describes how numerical magnitude allocation is subject to dynamic interhemispheric competition. That is, numerical allocation is continually updated in a contextual manner based upon relative magnitude, with the right hemisphere responsible for smaller magnitudes and the left hemisphere for larger magnitudes.

INTRODUCTION

It is postulated that for cultural innovations such as numbers, the brain co-opts evolutionarily older and multi-functional cortical circuits (Dehaene and Cohen 2007; Hubbard et al. 2005), particularly invoking fronto-parietal networks, repeatedly implicated for the allocation of spatial attention (Corbetta and Shulman 2002), eye movement control (Colby and Goldberg 1999; Duhamel, Colby, Goldberg 1992), perceptual switching during binocular rivalry (Lumer, Friston, Rees 1998), vestibular cortical processing (Dieterich et al. 2003) and numerical cognition (Cohen Kadosh, Lammertyn, Izard 2008; Knops et al. 2009; Piazza et al. 2004).

Specifically, numerical allocation has been shown to be linked with spatial attention mechanisms (Dehaene 1992; Fischer et al. 2003), whereby numerical magnitude is superimposed upon a left to right spatially oriented representation termed the mental number line (MNL) (Dehaene et al., 2003; Zorzi et al., 2002). This account is supported by the spatial numerical association of response code (SNARC) effect (Dehaene, Bossini, Giraux 1993) and the observation that shifts of spatial attention follow number perception in a magnitude-dependent fashion (Fischer et al. 2003). Further, a key line of evidence for this relationship arises from observations in stroke patients with left neglect, which occurs most frequently following right fronto-parietal lesions. Patients with neglect have been shown to have relative overinhibition of the lesioned hemisphere (Corbetta and Shulman 2011), and manifest a pathological numerical bias towards larger numbers (Umiltà, Priftis, Zorzi 2009; Vuilleumier, Ortigue, Brugger 2004; Zorzi, Priftis, Umiltà 2002).

However, other research is at odds with the numerical-spatial interactions outlined above. Firstly, the findings of Fischer and colleagues that shifts of spatial attention follow number

perception in a magnitude dependent fashion, have not been replicated in more recent

work (Zanolie and Pecher 2014). Further, a double dissociation between physical and

number line bisection has been reported, coupled with the demonstration that the

pathological number bias observed following lesions that lead to left spatial neglect, are

secondary to an impairment in working memory (Doricchi et al. 2005; Malhotra et al. 2005).

Moreover, a recent neuroimaging study demonstrated that numerosity is topographically

mapped but found no relationship to visuospatial responses (Harvey et al. 2013). Thus,

experimental data to-date, does not converge upon a coherent model of number-space

interaction in the human brain.

Of particular relevance to the work to be presented here is the finding that patients with left

spatial neglect whom manifest pathological numerical biases (Zorzi, Priftis, Umiltà 2002),

additionally exhibit an asymmetrical modulation of the vestibular-ocular reflex (VOR)

(Doricchi et al. 2002; Ventre-Dominey, Nighoghossian, Denise 2003). We have recently

demonstrated that it is possible to induce handedness-related asymmetrical cortical

modulation of the VOR experimentally in normal healthy subjects. This is achieved via a

physiological paradigm in which subjects experience binocular rivalry during concurrent

vestibular stimulation that elicits left- but not right-beating vestibular nystagmus. It is

currently thought that this asymmetrical modulation is associated with the relative

inhibition of the left hemisphere (Arshad et al. 2015; Arshad et al. 2014; Arshad,

Nigmatullina, Bronstein 2013; Horslen et al. 2014).

Accordingly, based upon the aforementioned results from neuropsychological studies and

the proposed overlapping neural networks between attentional mechanisms, vestibular

function and numerical cognition (Cohen Kadosh et al. 2007; Corbetta and Shulman 2002;

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Dehaene et al. 2003; Dieterich et al. 2003; Umiltà, Priftis, Zorzi 2009; van Elk and Blanke 2012), we hypothesised that numerical allocation would be subject to the same control mechanism underpinning both spatial attention and vestibular cortical processing, namely dynamic interhemispheric competition (Arshad et al. 2014; Szczepanski and Kastner 2013).

Here we directly tested this by examining firstly whether inducing an asymmetrical modulation of the VOR following unihemispheric inhibition (confirmed using targeted non-invasive brain stimulation) could result in numerical biases towards smaller numerical magnitudes during number pair bisection (Zorzi, Priftis, Umiltà 2002). Given that previous reports conflictingly suggest that number allocation may either be intertwined or disassociated with spatial attention mechanisms (Aiello et al. 2012; Zorzi, Priftis, Umiltà 2002), we also assessed whether any numerical bias was independent from, or directly related to, a lateralised spatial attentional bias. We subsequently aimed to corroborate our findings with a computational model of numerical cognition by applying it not only to our findings, but also to those of the SNARC effect (Dehaene, Bossini, Giraux 1993).

Taken together, this multi-method experimental approach allowed us to delineate the mechanisms underlying numerical magnitude allocation, and reconcile previous experimental data to propose a unified model of numerical cognition.

MATERIALS and METHODS

Experiment 1; Physiological manipulation of numerical magnitude and its relationship to a lateralised spatial attentional bias

The *general experimental strategy* consisted of experiencing binocular rivalry during concurrent vestibular stimulation via caloric irrigation (Arshad, Nigmatullina, Bronstein 2013; Arshad et al. 2013).

Vestibular stimulation

Participants lay supine upon a couch with the head tilted up by 30 degrees (to obtain

maximal horizontal semi-circular canal activation) and both knees were flexed to 45 degrees

to provide a writing surface support for the clock drawing experiments; see below (Figure

1A). The external auditory meatus was irrigated with water at either 30°C (cold) or 44°C

(warm) at a rate of 500 ml/min for 40 seconds (CHARTR VNG: ICS medical) (Figure 1B)

(Cawthorne, Fitzgerald, Hallpike 1942; Fitzgerald and Hallpike 1942).

Visual stimulation

As the experiment required the subjects to be darkness in order to prevent vestibular

suppression, binocular rivalry (BR) was induced using retinal afterimages (Blake 1989)

preceding the onset of vestibular activation. The rivalry device consisted of 2 LEDs

illuminated at 80 cd for a duration of 40s, positioned 42 cm directly in front of both eyes.

These 2 LEDs passed a point light source through two striated lenses (i.e. ophthalmic

Maddox rod) simultaneously, in order to generate a streak of light. A vertically orientated

light was projected in the right eye whilst a horizontally orientated light was projected in the

left eye (randomised between subjects) (Arshad et al. 2012). Viewing of the retinal

afterimages with eyes closed resulted in rivalry lasting for 3 minutes, with possible percepts

including vertical line (right eye image), horizontal line (left eye image) or a mixed-cross

percept (i.e. image from both eyes).

Experimental Tasks

The *experimental setup* remained constant for the *two tasks* that subjects performed. First,

subjects performed a *mental number pair bisection task*. Two numbers were presented

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through a loudspeaker situated in the midline directly behind the subject. Participants were required to estimate the mid-point without calculation. Participants had to respond within 3 seconds to ensure no calculations were made. For each test condition, 10 trials were provided (33-87), (39-93), (44-68), (48-92), (56-92), (59-87), (61-99), (67-95), (58-124) and (58-132). Each response was noted down by the experimenter and each of the trials was randomised between conditions (Zorzi, Priftis, Umiltà 2002). Bisection errors were calculated by subtracting the arithmetical midpoint from the reported midpoint given by the subjects and percentage bisection errors were calculated by dividing the errors by the number interval size (Zorzi, Priftis, Umiltà 2002). Positive mean % bisection errors denoted an overestimation, whereas negative mean % bisection errors denoted an underestimation from the actual midpoint. Number pair bisection was always performed in darkness for the three conditions (i.e. no stimulation (BASELINE), during caloric irrigation alone (CALORIC) and during caloric irrigation combined with rivalry stimulation (CALORIC+RIV)).

The second experimental task that subjects performed was ***clock drawing*** in order to assess for any possible lateralised spatial attentional bias. Subjects were asked to draw both numerical (1-12) and alphabetical (A-L; non-numerical control) clock-faces. Clock-faces were specifically chosen for their inherent right and left spatial layout, which is opposite to that found in the mental number line (Aiello et al. 2012). Subjects drew clocks in both clockwise (CW) and counter-clockwise (CCW) directions, without any part of the hand touching the paper (to prevent tactile cues). Clock-face drawings were always performed in darkness for each condition (BASELINE, CALORIC and CALORIC+RIV). Two different methods were employed to assess for distortion of clock drawings: Centre of Mass and inter-digit number spacing (see supplemental material 1).

Subjects

A total of 40 right-handed subjects participated (Handedness score over 40 (Oldfield 1971)) (22 female, age range 18-26 years, mean age 23 years). 20 subjects were recruited for the number pair bisection task and 20 different subjects for the clock-drawing task. In each experiment, 10 subjects participated in cold water irrigations and 10 in warm water irrigations. All subjects were naive to the purpose of study and had no history of otological, ophthalmological, psychiatric or neurological disorders. Written informed consent was provided as approved by the local ethics research committee.

RESULTS

As both vestibular stimulation and switching during rivalry-viewing have been shown to shift spatial attention, which in turn can modulate numerical cognition (Ferrè, Vagnoni, Haggard 2013; Fischer et al. 2003; Paffen and Van der Stigchel 2010; Rubens 1985), we first determined whether either vestibular stimulation alone or viewing binocular rivalry induced changes in number pair bisection. No effect of rivalry-viewing or vestibular activation alone was found upon number pair bisection [rivalry vs. no rivalry: $p > 0.05$, $F_{(2,18)} = 0.14$; vestibular stimulation vs no vestibular stimulation: $p > 0.05$, $F_{(2,18)} = 0.10$; left vs right caloric: $p > 0.05$, $F_{(2,18)} = 0.22$; Repeated Measures ANOVA].

We proceeded to examine whether the combination of rivalry-viewing and vestibular stimulation resulted in numerical biasing. During right ear cold irrigations that elicit left beating vestibular nystagmus combined with rivalry viewing (i.e. RIGHTCOLD+RIV), was found to bias subjects towards smaller numbers compared to the caloric alone condition (i.e. RIGHTCOLD) (Figure 2A) with a significant main effect of stimulation side [$p < 0.003$, F

(1,9) = 15.7, repeated measures ANOVA] and a significant interaction between rivalry and side of stimulation [p < 0.005, F (1,9) = 41.0]. Post hoc tests demonstrated a bias towards smaller numbers for the RIGHTCOLD+RIV condition (p < 0.001, paired t-test with Bonferroni correction) but no effect during left ear cold irrigations that elicits right beating vestibular nystagmus when combined with rivalry viewing (i.e. LEFTCOLD+RIV) (p = 0.71; Figure 2A). Conversely, when rivalry viewing was accompanied by left sided warm water irrigations, that elicit left beating vestibular nystagmus, there was a bias towards <u>larger</u> numbers compared to LEFTWARM caloric alone (p = 0.045, paired t-test with Bonferroni correction; Figure. 2B). No effect was observed during right-sided warm water irrigations (i.e. right beating vestibular nystagmus) when combined with rivalry viewing (RIGHTWARM+RIV) (p = 0.57; Figure 2B).

In order to address whether the above reported biases were primarily due to a lateralised spatial attentional bias, subjects drew both numerical and alphabetical clock-faces. If the numerical biasing we observed was directly coupled with spatial attention as per the MNL, we would expect that both numerical and alphabetical clocks would be distorted equally. Namely, we would expect a systematic leftward bias in the condition that lead to the bias towards smaller numbers (i.e. RIGHTCOLD+RIV), and a rightward bias in the condition that was associated with a bias towards larger numbers (i.e. LEFTWARM+RIV).

Figure 3 illustrates that numerical clocks drawn<u> clockwise</u> in the RIGHTCOLD+RIV condition were laterally displaced to the right hand side of space (Figure 3, and Supplemental Figure S2 upper panel). A 2x3 ANOVA examining displacement [factors: side (left, right), and condition (BASELINE, CALORIC, CALORIC+RIV)] showed no main effect for side, however there was a significant effect for condition [p < 0.001, F (2,18) = 12.3] and also an interaction

between side and condition [$p < 0.008$, $F(2,18) = 6.4$]. Post hoc tests revealed no effects for the RIGHTCOLD-only condition but a significant effect for RIGHTCOLD+RIV vs baseline ($p < 0.008$) and CALORIC+RIV vs caloric alone ($p = 0.005$, paired t-test Bonferroni adjusted; caloric-only vs baseline: $p = 0.73$; Figure 3). Conversely, numerical clocks for LEFTWARM+RIV <u>drawn anti-clockwise</u> were laterally displaced leftwards (Figure 3, and Supplemental Figure S2 lower panel). As in the previous analysis, ANOVA revealed a main effect of condition [$p < 0.0001$, $F(2,18) = 21.7$] and a significant interaction between side and condition [$p < 0.003$, $F(2,18) = 8.4$]. Post hoc tests demonstrated no effect for the LEFTWARM-only condition but a significant effect between LEFTWARM+RIV vs baseline ($p < 0.001$), CALORIC+RIV vs caloric alone ($p < 0.007$) (see Figure 3).

Notably, neither RIGHTWARM+RIV nor LEFTCOLD+RIV conditions distorted numerical clock drawings. Critically, drawing alphabet clocks clockwise during cold caloric irrigation showed no significant effect of the side of the irrigation ($F(2,18) = 0.08$, $p > 0.05$) or condition (BASELINE, CALORIC, CALORIC+RIV; $F(2,18) = 1.29$, $p > 0.05$, 2x3 ANOVA). Similarly, no significant effects were found during warm caloric irrigation (side: $F(2,18) = 0.001$, $p > 0.05$; conditions: $F(2,18) = 5.1$, $p > 0.05$). For anticlockwise alphabet clock drawings, there were also no significant effects found for either cold (side: $F(2,18) = 0.031$, $p > 0.05$; conditions: $F(2,18) = 1.1$, $p > 0.05$) or warm caloric irrigations (side: $F(2,18) = 0.34$, $p > 0.05$; conditions: $F(2,18) = 2.0$, $p > 0.05$).

Our prediction in Experiment 1 was that both RIGHTCOLD+RIV and LEFTWARM+RIV conditions would modulate numerical cognition in the same direction, as we predicted that in both of these conditions, following interhemispheric conflict, one would expect inhibition of the same hemisphere (i.e. left hemisphere) (Arshad et al. 2015; Arshad et al. 2014).

However, we serendipitously observed a differential modulation of numerical allocation, as RIGHTCOLD+RIV biased subjects towards smaller numbers, whereas LEFTWARM+RIV biased subjects towards larger numbers. Moreover, clockface drawings were also distorted and laterally displaced in opposing directions by the two conditions.

These results raise the critical question as to why RIGHTCOLD+RIV and LEFTWARM+RIV led to opposing effects. The underlying principle of this technique is that during concurrent visuo-vestibular stimulation it is possible to selectively induce interhemispheric conflict solely by altering the vestibular stimulus (Arshad et al. 2013). Previous studies implementing either functional imaging approaches or behavioural neuro-modulatory techniques have shown that neural activity associated with perceptual switching during binocular rivalry is tightly linked to the fronto-parietal network, predominantly in the right hemisphere (Carmel et al. 2010; Corbetta and Shulman 2002; Knapen et al. 2011; Lumer, Friston, Rees 1998; Zaretskaya et al. 2010). Moreover, we have shown both previously and herein (see supplemental material 3) that identical effects can be obtained if other visuospatial paradigms that call upon the right hemisphere are combined with vestibular stimulation (Arshad et al. 2013; Arshad, Nigmatullina, Bronstein 2013). Interhemispheric conflict is induced when the vestibular component is predominantly processed in the left hemisphere (i.e. a right-sided cold (RIGHTCOLD) or left-sided warm (LEFTWARM) caloric irrigation), (Dieterich et al. 2003; Lopez, Blanke, Mast 2012; Suzuki et al. 2001; Zu Eulenburg et al. 2012). In the aforementioned scenarios an asymmetrical VOR is induced (Arshad et al. 2013) but when vestibular stimulation induces predominantly right-hemisphere activation, (i.e. left-sided cold (LEFTCOLD) or right-sided (RIGHTWARM) irrigations) (Dieterich et al. 2003; Lopez, Blanke, Mast 2012; Suzuki et al. 2001; Zu Eulenburg et al. 2012) there is no interhemispheric conflict, as both the vestibular and visual components preferentially

activate the same hemisphere. Accordingly, we hypothesized that these opposing effects were attributable to the comparative difference in the degree of left hemisphere vestibular activation during RIGHTCOLD and LEFTWARM irrigations respectively (Figure 4) (Akbarian et al. 1988; Akbarian, Grüsser, Guldin 1992; Akbarian, Grüsser, Guldin 1993; Akbarian, Grüsser, Guldin 1994). This relative difference would then, via an 'all-or-nothing' effect, determine which hemisphere is inhibited by concurrent visuo-vestibular stimulation. We directly tested this hypothesis in experiment 2.

Experiment 2; Using tDCS to probe the neural correlates of the asymmetrical VOR modulation

To test the above hypothesis we applied unipolar tDCS over the frontal eye fields to either augment or attenuate the VOR asymmetries following CALORIC+RIV stimulation. This region was chosen as the stimulation site as it has previously been demonstrated as a critical node in frontoparietal networks underlying numerical processing, vestibular processing and for the control of spatial attention (Corbetta et al. 2005; Fasold et al. 2002; Husain and Kennard 1996; Jahanshahi et al. 2000; Kluge et al. 2000; Nieder 2005; Nieder and Dehaene 2009; Nieder and Miller 2004). Crucially, unlike parietal tDCS alone, direct stimulation of the frontal eye fields do not lead to modulation of the VOR (Arshad et al. 2015; Arshad et al. 2014). Thus, any effect on the VOR would be secondary to modulation of interhemispheric interactions rather than any direct influence on vestibular processing. During this experiment participants were exposed to identical stimulation conditions to those employed in Experiment 1, with simultaneous eye-movement recording. (Arshad, Nigmatullina, Bronstein 2013; Arshad et al. 2013). We predicted that, if the right hemisphere was primarily involved in mediating the VOR modulation during the RIGHTCOLD+RIV condition,

then unipolar anodal (i.e. excitatory) stimulation of the right hemisphere and unipolar

cathodal stimulation (i.e. inhibition) of the left hemisphere would augment the VOR

asymmetries, whereas unipolar left hemisphere anodal and unipolar right hemisphere

cathodal stimulation would lead to attenuation. If the left hemisphere were mediating the

effects during the LEFTWARM+RIV condition, we would expect the opposite effects:

attenuation of VOR asymmetries with unipolar anodal stimulation of the right hemisphere

and unipolar cathodal stimulation of the left hemisphere and augmentation with unipolar

left hemisphere anodal and unipolar right hemisphere cathodal stimulation.

Eye movement recording

LEFTCOLD and RIGHTWARM irrigations elicit right-beating nystagmus, whereas LEFTWARM

and RIGHTCOLD elicit left-beating nystagmus (Cawthorne, Fitzgerald, Hallpike 1942;

Fitzgerald and Hallpike 1942). The oculomotor response following vestibular stimulation was

tracked using a head mounted infra-red binocular video-oculography (VOG) system. An

automated computerised programme (CHARTR VNG; ICS medical) removed the fast phases

from the nystagmus waveform, allowing us to plot the velocity of each slow phase over 120

seconds (Figure 1B). Response intensity was determined by obtaining the mean peak slow

phase eye velocity (Barnes 1995).

Trans-cranial direct current stimulation (tDCS)

A battery driven stimulator (neuroConn GMBH, Ilmenau, Germany) was used to apply

stimulation. The current had a ramp up time of 10 seconds at which point a constant current

of 1.5 mA was applied for a duration of 15 minutes. At the end of the stimulation the

current was ramped down in a 10 second fade out period. The uni-hemispheric tDCS

montage chosen was the same as that used in a previous study that targeted the frontal eye

fields that lie within the dorsolateral pre-frontal cortex (dLPFC) (Kanai, Muggleton, Walsh 2012). Electrode positions were defined using 10-20 international EEG electrode placement co-ordinates. That is, for either ANODAL or CATHODAL stimulation of the right hemisphere the electrode was placed over F4 (10-20 EEG co-ordinate), whilst for either ANODAL or CATHODAL stimulation of the left hemisphere the electrode was placed over F3 (10-20 EEG co-ordinate). The reference electrode was always placed over the ipsilateral shoulder (deltoid muscle) (Kanai, Muggleton, Walsh 2012).

Experimental protocol

Firstly, we demonstrated that when binocular rivalry is combined with left-beating vestibular nystagmus, it induces an asymmetrical VOR (Arshad, Nigmatullina, Bronstein 2013). Two groups of 10 right handed subjects (Handedness score over 40) were recruited; group 1: cold water irrigations (5 Males; age range 20-26, mean age 21.9); group 2: warm water irrigations (6 Females; age range 20-24, mean age 21.3). Both groups underwent 4 conditions in total: cold (group 1) or warm (group 2) CALORIC alone on the right, cold (group 1) or warm (group 2) CALORIC alone on the left, cold (group 1) or warm (group 2) RIGHTCALORIC+RIV and cold (group 1) or warm (group2) LEFTCALORIC+RIV. In each condition we established the peak SPV. We compared the peak SPV for the CALORIC+RIV condition with the corresponding CALORIC alone condition (Arshad et al. 2014).

In the second part of the experiment we modulated cortical excitability using unipolar frontal tDCS in 4 separate randomised sessions, with each session separated by 4 days to avoid carry-over effects. For each group, we assessed VOR asymmetries following both right hemisphere anodal or cathodal stimulation, and both left hemisphere anodal or cathodal stimulation.

RESULTS

For group 1, a 2x2 repeated measures ANOVA with binocular rivalry (two levels; binocular rivalry, no binocular rivalry) and laterality of caloric (two levels; left ear, right ear) indicated a significant main effect of binocular rivalry ($F[1,9]$ = 34.5, $P < 0.0001$), no main effect of laterality ($F[1,9]$ = 1.2, $P > 0.05$), and a significant interaction between laterality*rivalry ($F[1,9]$ = 7.8, $P = 0.021$) (Figure 5). Post-hoc paired t-tests (Bonferroni corrected) revealed a significant difference between RIGHTCOLD alone and RIGHTCOLD+RIV ($P < 0.0001$; paired t-test). No effect was observed for LEFTCOLD irrigations ($P > 0.05$; paired t-test). In group 2, a separate 2x2 repeated measures ANOVA with binocular rivalry (two levels) and laterality of caloric (two levels) indicated a significant main effect of rivalry ($F[1,9]$ = 8.1, $P = 0.019$), no significant main effect of laterality ($F[1,9]$ = 1.0, $P > 0.05$), and a significant interaction between laterality*rivalry ($F[1,9]$ = 8.7, $P = 0.016$) (Figure 5). Post-hoc paired t-tests (Bonferroni corrected) revealed a significant difference between LEFTWARM alone and LEFTWARM+RIV ($P < 0.0001$; paired t-test). No effect was observed for RIGHTWARM irrigations ($P > 0.05$; paired t-test).

For the second part of the experiment, a 2x2x2x2 repeated measures ANOVA for group 1 was employed, with factors SIDE (2 levels; right ear or left ear), RIVALRY (two levels; binocular rivalry or no binocular rivalry), STIMULATION TYPE (2 levels; cathodal or anodal) and STIMULATION SIDE (2 levels; left hemisphere or right hemisphere). This revealed a significant main effect for caloric side ($F[1,9]$ = 129, $P < 0.001$), significant main effect of binocular rivalry ($F[1,9]$ = 20.70, $P < 0.001$), no main effect for stimulation type ($F[1,9]$ = 1.7, $P > 0.05$) and a significant main effect for stimulation side ($F[1,9]$ = 4.97, $P = 0.04$). There was a significant 4-way interaction between side*rivalry*stimulation type*stimulation side

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(F[1,9] = 89.19, P < 0.0001) (Figure 6A). Post hoc paired t-tests (Bonferroni corrected) revealed that in the RIGHTCOLD+RIV condition, application of either right hemisphere anodal stimulation or left hemisphere cathodal stimulation induced asymmetrical modulations of the VOR (P < 0.001; paired t-test). No asymmetries of the VOR were induced for the RIGHTCOLD+RIV condition following either right hemisphere cathodal or left hemisphere anodal stimulation (P > 0.05; paired t-test). Further, no effect for LEFTCOLD irrigations were observed in any of the tDCS conditions (P > 0.05; paired t-test) (Figure 6A).

As in the previous analysis, a 2x2x2x2 repeated measures ANOVA for group 2, revealed a significant main effect for caloric side (F[1,9] = 137.4, P < 0.001), significant main effect of binocular rivalry (F[1,9] = 24.6, P < 0.001), no main effect for stimulation type (F[1,9] = 0.835, P > 0.05) and a significant main effect for stimulation side (F[1,9] = 3.84, P = 0.047). There was a significant 4-way interaction between side*rivalry*stimulation type*stimulation side (F[1,9] = 77.17, P < 0.0001) (Figure 6B). Post hoc paired t-tests (Bonferroni corrected) revealed that in the LEFTWARM+RIV condition, application of either right hemisphere cathodal stimulation or left hemisphere anodal stimulation induced asymmetrical modulation of the VOR (P < 0.001; paired t-test). No asymmetries of the VOR were induced for the LEFTWARM+RIV condition following either right hemisphere anodal or left hemisphere cathodal stimulation (P > 0.05; paired t-test). Further, no effect for RIGHTWARM irrigations were observed in any of the tDCS conditions (P > 0.05; paired t-test) (Figure 6B).

Taken together, these results provide strong evidence that in the two conditions that induce interhemispheric conflict and subsequent asymmetrical modulation of the VOR, namely RIGHTCOLD+RIV and LEFTWARM+RIV, there is selective inhibition of the left and right

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hemispheres, respectively. That is, during RIGHTCOLD+RIV the asymmetrical modulation of the VOR is mediated by the right hemisphere, as anodal stimulation of the right hemisphere and cathodal stimulation of the left hemisphere augment the VOR asymmetries, whereas left hemisphere anodal and right hemisphere cathodal stimulation attenuate the VOR asymmetries (Figure 4 and 6). Conversely, during LEFTWARM+RIV the asymmetrical modulation of the VOR is mediated by the left hemisphere, as left hemisphere anodal stimulation and cathodal stimulation of the right hemisphere augment the VOR asymmetries whereas left hemisphere cathodal or right hemisphere anodal stimulation attenuate the VOR asymmetries (Figure 4 and 6). Hence, these findings are in keeping with the results of Experiment 1 and provide an explanation for the opposing effects upon number allocation of right-sided cold water irrigation and left-sided warm water irrigation, when combined with binocular-rivalry viewing. Accordingly, we proceeded to examine the precise relationship between induced VOR asymmetries, uni-hemispheric inhibition and numerical magnitude allocation in experiment 3.

Experiment 3; Relationship between uni-hemispheric inhibition, induced VOR asymmetries and numerical magnitude allocation

Experiment 3a) Relationship between VOR asymmetries and numerical biases

In the above group of subjects (i.e. those that participated in Experiment 2) we proceeded to examine the relationship between the degree of VOR suppression induced by either the RIGHTCOLD+RIV or LEFTWARM+RIV conditions respectively, upon both (i) each individuals mean number pair bisection error (%) and (ii) the size of the lateral shift induced in the centre of mass for the numerical clock drawings.

As shown in Figure 7, we observed a significant negative correlation between number pair bisection error (%) and the degree of vestibular nystagmus suppression following RIGHTCOLD+RIV (R^2 0.6774, p < 0.01 Pearson's correlation), whereas following LEFTWARM+RIV we observed a significant positive correlation (R^2 0.86, p < 0.01 Pearson's correlation). That is, following RIGHTCOLD+RIV, the individuals that exhibit greater degree of vestibular nystagmus suppression demonstrated a more pronounced numerical bias towards smaller numbers. Conversely, following LEFTWARM+RIV, individuals who exhibited greater vestibular nystagmus suppression demonstrated a more pronounced numerical bias towards larger numbers (Figure 7). These finding are in line with our recent observations, which demonstrate that interhemispheric asymmetries as reflected by vestibular nystagmus suppression, can directly predict individual differences in line bisection error (i.e. pseudoneglect) (Arshad et al., in press).

With respect to the numerical clock drawings, the larger the rightward lateral shift during RIGHTCOLD+RIV, the greater the vestibular nystagmus suppression (R^2 0.7974, p < 0.01 Pearson's correlation). During LEFTWARM+RIV, a greater degree of vestibular nystagmus suppression was associated with a more pronounced leftward lateral shift (R^2 0.6991, p <0.01 Pearson's correlation) (Figure 8).

The above data directly demonstrates that a correlative relationship exists between the numerical effects observed in experiment 1 and the degree of eye movement suppression induced by the CALORIC+RIV stimulation, as tested in part 1 of Experiment 2 (i.e. Figure 5). Having established this relationship, we proceeded to apply frontal tDCS in order to modulate the VOR asymmetries, as per the stimulation paradigm in the second part of Experiment 2, to ascertain its impact upon numerical magnitude perception.

Experiment 3b; Using tDCS to probe the neural correlates of numerical magnitude allocation To specifically ascertain the neuro-anatomical correlates of numerical magnitude allocation, following CALORIC+RIV stimulation we applied unipolar frontal tDCS. During this experiment, participants were exposed to an identical stimulation paradigm and experimental task (i.e. number pair bisection task) to that employed in Experiment 1.

We predicted that, if relative unihemispheric inhibition following hemispheric conflict was responsible for the numerical biases, then tDCS, by increasing or decreasing the degree of resultant unihemispheric inhibition, would augment or reverse the numerical bias in the conflict conditions (i.e. RIGHTCOLD+RIV and LEFTWARM+RIV) with a directional specificity. Moreover, we predicted that simply modulating cortical excitability via application of tDCS either alone or in the no-conflict conditions (i.e. LEFTCOLD+RIV and RIGHTWARM+RIV) would have no effect upon numerical magnitude allocation.

Application of unipolar tDCS alone had no effect upon number pair bisection error. A 2x2 repeated measures ANOVA revealed no main effect for either side of stimulation ($F_{[9,1]} = 0.110$ $p> 0.05$) nor type of stimulation ($F_{[9,1]}$ 2.276 $p> 0.05$) (Figure S4; supplemental data). Subsequently, to assess the effects of tDCS upon number pair bisection during the CALORIC+RIV conditions, we recruited two groups of 10 right handed subjects (Handedness score over 40). Group 1 participated in cold water irrigations (6 Males; age range 19-26, mean age 22.7), whereas group 2 participated in warm water irrigations (4 Females; age range 20-28, mean age 23.3). For each group, we compared the number pair bisection error during CALORIC+ RIV stimulation relative to the corresponding caloric alone condition, both before and after tDCS. Cortical excitability was modulated using unipolar frontal tDCS as performed in experiment 2. This constituted 4 separate randomised sessions (i.e. right

hemisphere anodal or cathodal stimulation, and left hemisphere anodal or cathodal stimulation), with each session separated by 4 days to avoid any potential carry-over effects.

For group 1, a 2x2x2x2 repeated measures ANOVA was employed, with factors TYPE of stimulation (2 levels; anodal or cathodal), SIDE of stimulation (2 levels; right or left), IRRIGATION side (2 levels; right or left) and TIME (2 levels; number pair bisection error either before or after tDCS). This revealed a significant main effect for TIME ($F[1,9]=21.4$, $p<0.001$), a significant main effect for IRRIGATION side ($F[1,9]=47.49$, $p<0.000$), a significant main effect for SIDE of stimulation ($F[1,9]=2.41$, $p<0.05$), but no main effect for TYPE of stimulation ($F[1,9]=0.018$, $p>0.05$). There was a significant 4-way interaction between type*side*irrigation*time ($F[1,9]=59.149$, $P < 0.0001$) (Figure 9C). Post hoc paired t-tests (Bonferroni corrected) revealed that in the RIGHTCOLD+RIV condition, application of either right hemisphere anodal stimulation or left hemisphere cathodal stimulation augmented the numerical biases towards smaller numbers ($P < 0.001$; paired t-test). Further, during RIGHTCOLD+RIV, the numerical biasing towards smaller numbers was abolished following either right hemisphere cathodal or left hemisphere anodal stimulation ($P > 0.05$ paired t-test) (Figure 9C). No effects upon number pair bisection error were observed for LEFTCOLD irrigations in any of the tDCS conditions ($P > 0.05$; paired t-test) (Figure 9D).

For group 2, as in the previous analysis, a 2x2x2x2 repeated measures ANOVA revealed a significant main effect for TIME ($F[1,9]=30.49$, $p<0.0001$), a significant main effect for IRRIGATION side ($F[1,9]=90.7$, $p<0.0001$), a significant main effect for SIDE of stimulation ($F[1,9]=0.2193$, $p< 0.05$), but no main effect for TYPE of stimulation ($F[1,9]=0.153$, $p>0.05$). There was a significant 4-way interaction between type*side*irrigation*time ($F[1,9] = 287.53$, $P < 0.0001$) (Figure 9B). Post hoc paired t-tests (Bonferroni corrected) revealed that

in the LEFTWARM+RIV condition, application of either left hemisphere anodal stimulation or right hemisphere cathodal stimulation augmented the numerical biases towards larger numbers (P < 0.001; paired t-test). Further, during LEFTWARM+RIV, the numerical biasing towards larger numbers was abolished following either left hemisphere cathodal or right hemisphere anodal stimulation (P > 0.05; paired t-test). No effects upon number pair bisection error were observed for RIGHTWARM irrigations in any of the tDCS conditions (P > 0.05; paired t-test) (Figure 9A).

Taken together, we provide a direct demonstration that RIGHTCOLD+RIV results in left hemisphere inhibition and numerical biases towards smaller numbers, whereas LEFTWARM+RIV results in right hemisphere inhibition which biases judgements towards larger numbers.

Experiment 4 Computational model of numerical allocation

Following on from the findings that left hemisphere inhibition was associated with numerical biasing towards smaller numbers and right hemisphere inhibition with bias towards larger numbers, we sought a mathematical model that could predict the biases observed. We implement x to denote the percentage error in midpoint bisection and *p(x)* to denote the probability of this error. The distribution *p(x)* is affected only by the hemispheric conflict conditions (i.e. RIGHTCOLD+RIV and LEFTWARM+RIV). Total stimulation of the right hemisphere is denoted by *r* and total stimulation of the left hemisphere by *l*. The probability of making an error *p(x)* in the bisection task depends on both *r* and *l* (i.e. *p(x) = p(x;l,r)*). We implement a statistical mechanical model, such that for *p(x;l,r)* we can represent it as a Boltzmann weight, whereby β is the parameter specifying the width of the probability

distribution and *E(x;l,r)* is a function (i.e. energy). The denominator applied in equation [1] is

a normalization factor.

$$p(x; l, r) = \frac{\exp(-E(x; l, r)\beta)}{\int_{-\infty}^{\infty} \exp(-E(x; l, r)\beta) \, dx}, [1]$$

The choice of the function E(x;l,r) completes the construction of the model as follows:

$$E(x; l, r) = (1 - lr)x^2 + (-l^2r + lr^2)x + (1 + lr)x^4, [2]$$

Both equations [1] and [2] can completely define the model and allow the calculation of

various bisection errors based upon the strength of right and left hemisphere activation

respectively. Each term in equation [2] has a physical meaning so that the first term is

quadratic in *x* and when either *l* or *r* or both are equal to zero, it simply penalizes any

deviations from the optimal value *x=0* as found during no hemispheric conflict conditions

(i.e. LEFTCOLD+RIV   or RIGHTWARM +RIV). In hemispheric conflict conditions (i.e.

RIGHTCOLD+RIV or LEFTWARM +RIV), both *l* and *r* are concurrently non-zero leading to the

bisection error shifts. During conflict, having *x=0* is no longer the optimum value and the

most likely bisection error is shifted towards either smaller or larger numbers. Due to the

second term in equation [2] the shift observed is asymmetric. That is, in conflict situations

only the relatively greater activation of the right hemisphere results in a bisection error shift

towards smaller numbers (negative direction), whereas left hemisphere activation following

conflict shifts the error in the positive direction (i.e. larger numbers). The last term in

equation [2] is implemented in order to ensure that very large deviations of *x* from zero are

unfavorable, even in the presence of large interhemispheric conflict (i.e. ceiling effect).

Figure 10 illustrates several calculated probability distributions that correspond to a fixed

value of *r* but different values of *l* and hence varying degree of the interhemispheric

competition. When *r* and *l* are equal, either hemisphere may be preferentially activated. Accordingly, the subject is equally likely to make errors in either the positive or negative direction. In order to confirm that the model generalized to other experimental findings, we verified it by applying it to the most influential account of lateralized processing and numerical cognition: the SNARC effect (Dehaene, Bossini, Giraux 1993) (see supplemental material 6).

DISCUSSION

Using an innovative multi-method approach to induce dynamic interhemispheric competition in neurologically intact individuals, we sought to investigate how the brain controls numerical magnitude. Implementation of this methodology allowed us to avoid the associated confounds of previous studies that have probed numerical cognition in brain-damaged individuals, namely spatial neglect and impairment of working memory (Aiello et al. 2012; Malhotra et al. 2005; Zorzi et al. 2006).

Here we provide the first demonstration of a systematic bidirectional modulation of numerical magnitude towards either lower or higher numbers. This only occurred during those stimulation conditions that induced interhemispheric conflict (i.e. combining binocular rivalry with either right-sided cold caloric vestibular irrigation or left-sided warm caloric vestibular stimulation respectively) (Arshad et al. 2013; Arshad, Nigmatullina, Bronstein 2013).

Indeed, the absence of any significant numerical modulation following either vestibular or visual stimulation alone compared to baseline and, critically, during the "no conflict" conditions (i.e. RIGHTWARM+RIV and LEFTCOLD+RIV conditions), rules out the possibility

that numerical biases were secondary to generalised arousal effects, dizziness or visuo-vestibular mismatch (Arshad et al. 2013). Further, substituting the binocular rivalry with a visuospatial working memory task (see supplemental material 3) demonstrates that these effects are not specific to binocular rivalry per se, but rather reflect a generalised involvement of the right lateralised fronto-parietal visuospatial attentional network (Arshad, Nigmatullina, Bronstein 2013; Corbetta and Shulman 2002; Lumer, Friston, Rees 1998; Miller et al. 2000). Critically, as right-sided cold and left-sided warm water irrigations both elicit left-beating vestibular nystagmus (Barnes 1995; Cawthorne, Fitzgerald, Hallpike 1942; Fitzgerald and Hallpike 1942); it was found that when these irrigations were combined with visual stimulation, it modulated numerical magnitude in opposing directions. Hence, eye movements can also be ruled out as the cause of the observed numerical biasing (Loetscher et al. 2010).

Accordingly, the results from experiments 1, 2 and 3 provide a direct demonstration that the numerical biases observed following our physiological manipulations resulted from relative unihemispheric inhibition. That is, during the LEFTWARM+RIV condition, there is a left hemisphere-predominant response with associated right hemisphere inhibition, and subsequent biasing towards larger numbers. This is in keeping with the observations that pathological biases towards higher numbers occur during large interval number-pair bisection tasks (as implemented herein), following lesions that result in a rightward attentional bias (Zorzi, Priftis, Umiltà 2002; Zorzi et al. 2006). In contrast, during RIGHTCOLD+RIV there is left hemisphere inhibition following interhemispheric conflict, resulting in biasing of numerical judgements towards smaller numbers. This account is additionally corroborated by our computational model, which suggests that numerical allocation is subject to dynamic interhemispheric competition, and predicts not only the

results of our stimulation paradigm but also those of the SNARC effect (see supplemental

material 6) (Dehaene, Bossini, Giraux 1993).

Given that previous reports have demonstrated a close link between spatial attention and

numerical control mechanisms (Dehaene, Bossini, Giraux 1993; Umiltà, Priftis, Zorzi 2009;

Zorzi, Priftis, Umiltà 2002), one possible account for our findings is that they are secondary

to shifts in spatial attention (Fischer et al. 2003). Indeed, our data from the number pair

bisection task is in line with the vast majority of previous studies in numerical cognition, in

that it appears to suggest an inherent link between number and space (Hubbard et al. 2005;

Stoianov et al. 2008; Umiltà, Priftis, Zorzi 2009). However, to directly probe numerical-

spatial interactions, we asked subjects to reproduce culturally neutral clock-faces. In the

conventional representation of both clock faces and the MNL there is an inherent left and

right side, but importantly, numbers in each are mapped on to the opposite sides of space.

That is, in the MNL small numbers are found on the left side of space, whereas on a clock

face smaller numbers are represented on the right side of space (Aiello et al. 2012).

Intriguingly we observed that the distortions of the clock drawings were in the 'opposite'

direction to those observed during the number pair bisection task. Hence, the results of the

clock drawings provide strong evidence that the numerical effects observed are not directly

linked to a spatially lateralised attentional bias for three principle reasons. Firstly, the lateral

displacements that we observed followed a directional bias opposite to that which would be

expected from a spatially lateralised effect following the relative inhibition of each

hemisphere (Kinsbourne 1977; Szczepanski, Konen, Kastner 2010). Secondly, the critical

absence of any systematic displacement in the alphabet clock conditions demonstrates that

these effects, as in the study by Aiello and colleagues, are primarily numerical in origin

rather than secondary to any lateralized bias of spatial attention (Aiello et al. 2012). Thirdly, in a supplemental experiment, we observed no differences in straight ahead pointing ability when comparing any of the CALORIC+RIV conditions to their corresponding Caloric only conditions (see supplemental material 7).

Further support for the above viewpoint stems from previous work demonstrating that spatial attention shifts following the elicitation of nystagmus, can be coupled to either the slow (Rubens 1985) or fast phase (Figliozzi et al. 2005; Figliozzi et al. 2010; Teramoto et al. 2004; Watanabe et al. 2011) component of the eye movement. The direction of the shift appears to be dependent upon the stimulus employed to elicit the nystagmic eye movement. Regardless of whether the shifts in spatial attention occur in the direction of the fast or slow phase, the fact remains that as both RIGHTCOLD+RIV and LEFTWARM+RIV conditions induce left-beating nystagmus, they were associated with numerical biasing in opposing directions. This provides further direct support for a dissociation between numerical and spatial biases, however, our results are in apparent contrast to those of a recent study that employed passive whole-body vestibular stimulation (Hartmann, Grabherr, Mast 2012). Namely, Hartmann and colleagues demonstrated a bidirectional relationship between the generation and processing of numerical magnitude and self-motion detection, supporting the view that a close relationship exists between spatial attention and numerical control mechanisms (Dehaene, Bossini, Giraux 1993; Umiltà, Priftis, Zorzi 2009; Zorzi, Priftis, Umiltà 2002). We propose that these opposing findings are due to the fact that numerical-spatial links are much more likely to be generated when the task requires left-to-right coding of motor responses, as opposed to purely verbal responses that do not require directional specific motor coding (Rotondaro et al. 2015).

The notion that at least some degree of dissociation in certain circumstances can exist between numerical magnitude and spatial attention mechanisms has been hinted at in previous findings from right brain damaged individuals (Aiello et al. 2012; Doricchi et al. 2005; van Dijck et al. 2011). Indeed, such dissociation has recently been demonstrated in a study where numerosity was shown to be topographically mapped in the parietal lobe, but critically with no relationship to visuo-spatial responses (Harvey et al. 2013). However, it has been argued that this finding was potentially confounded due to variability introduced by non-numerical sensory cues associated with numerosity (Gebuis, Gevers, Cohen Kadosh 2014). We observed that in the condition that resulted in preferential activation of the right hemisphere (i.e. RIGHTCOLD+RIV), the numerical clocks showed an expansion for the spatial representation devoted to smaller numbers (i.e. increased spacing between these numbers) and compression of space between larger numbers. The converse was found for numerical clock drawings during preferential activation of the left hemisphere (i.e. LEFTWARM+RIV). That is, we observed increased spacing between larger numbers and compression of space between smaller numbers. Note, that individual differences in inter-digit spacing were not related to hand dominance (see supplemental material 5). Thus, our results, using Arabic notated numerical magnitude, hence avoiding the associated confound of non-numerical sensory cues, provide the first demonstration that numerical magnitude is topographically mapped at the cortical level.

Taken together, our data provides the underpinnings of a coherent model to explain numerical magnitude allocation in the human brain. Our findings demonstrate that the right hemisphere is disproportionately responsible for the allocation of smaller numbers, suggestive of a cortical magnification factor. We propose that the MNL can be equated to context-dependent encoding of small numbers in association with the left side of space

through disproportionate representation in the right hemisphere, with larger numbers being represented in association with rightward space in the left hemisphere. Because of this lateralization of numerical encoding and the similarity of the mechanisms underpinning numerical allocation as well as spatial attention, under most circumstances smaller numbers are associated with the left side of space and larger numbers with the right side. However, in specific experimental conditions, there can be dissociation between number size and side of space. Hemispheric numerical magnitude allocation appears to be continually updated in a relative manner, rather than inherently associated with a particular hemisphere.

To conclude, using a multi-method approach in neurologically intact individuals, we provide the first demonstration of a bidirectional modulation of numerical magnitude and have demonstrated the pivotal role of dynamic interhemispheric competition for numerical allocation and representation in the human brain. Our proposed model provides a clear account for our results as well as previous key findings in the field, and opens the way for future studies to further explore the relationship between interhemispheric interactions and number allocation.

AUTHOR CONTRIBUTIONS

Q.A. conceptualised study; Q.A Y.N A.M.B and PM designed the experiments. Q.A. P.A. performed the number pair bisection and clock drawing (i.e. motor transformation) experiments. Q.A S.S U.G performed the tDCS number experiment. R.E.R P.A. Y.N. S.S and U.G. performed analysis and statistics for visuo-motor transformation task. Q.A. S.K K.S and S.S performed the tDCS eye movement experiment   Y.N. performed analysis and statistics for mental number line bisection task. R.N. performed computational modelling. Y.N.

prepared all figures for the manuscript. Q.A. P.M. wrote the manuscript. Y.N, U.G, R.E.R,

R.C.K., A.M.B. edited the manuscript; R.C.K. provided critical input and expertise in analysis

and interpretations of the results. A.M.B. and P.M. supervised the project.

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Figure legends

Figure 1 Experimental set up for number pair bisection and clock drawing (i.e. motor transformation) tasks. **A** Subjects lay supine with the head tilted up by 30 deg and with the knees flexed at 45 deg. The binocular rivalry ('RIV') was delivered using afterimages. A board was rested on the subject's thighs to provide writing support for the clock drawings. **B** Caloric irrigation (either cold 30°C or warm 44°C water irrigations) were applied to either the right (R) or left (L) ear for a duration of 40 sec. Immediately at the end of the caloric irrigation, subjects performed either the mental number pair bisection task or clock drawings (Experiment 1). The vestibular activation in response to a caloric evokes nystagmus at around 20 sec as represented by slow phase velocity, eye movement trace (in red; schematically drawn based on our normative data) (Experiment 2). In the CALORIC+RIV

condition, the binocular rivalry ('RIV') was applied before the onset of the caloric and lasted for the entire duration of the task.

Figure 2 Results from mental number pair bisection experiments following physiological manipulations. We present the mean % bisection error from the midpoint of the numerical interval. **A** 'Caloric+RIV' condition (grey diamonds) resulted in subjects significantly underestimating the midpoint (i.e. shift to the left as indicated by red arrow) when compared to 'Caloric-only' (black diamonds) condition following RIGHTCOLD+RIV (LOWER PANEL), but no effect was found during LEFTCOLD+RIV (UPPER PANEL). **B** During LEFTWARM+RIV the subjects demonstrated a significant shift towards larger numbers (i.e. rightward shift as indicated by red arrow), suggesting overestimation of the midpoint (upper panel). No effect of RIGHTWARM+RIV was observed (LOWER PANEL). Grey shaded area in panels indicates 95% confidence limits calculated from baseline measures (i.e. no caloric or vestibular stimulation). Dashed line at 0 corresponds to 0% error i.e. accurate bisection. Data marked ** is significant at $p < 0.01$; data marked * is significant at $p < 0.05$. Error bars indicate standard errors.

Figure 3 Grand average results from the clock-drawing task presented as heat maps (upper panel) and centre of mass analysis (bottom panel). **A** (LEFT PANEL) Following RIGHTCOLD+RIV when subjects were asked to draw the clocks clockwise (CW), a significant shift to the right (indicated by red arrow) is seen in the 'Caloric + RIV' condition (grey diamonds) compared to 'caloric alone' (black diamond) condition. **B** (RIGHT PANEL) Following LEFTWARM+RIV when subjects were asked to draw the clock anticlockwise (ACW), a significant shift to the left (indicated by red arrow) was observed in 'Caloric + RIV' (grey diamonds) compared to 'caloric alone' (black diamond) condition. Grey shaded area in lower panels indicates 95% confidence limits calculated from baseline measures (i.e. no caloric or vestibular stimulation). Dashed line at 0.5 indicates the midline of a perfectly symmetrical clock. Data marked ** is significant at $p < 0.01$. Error bars indicate standard errors.

Figure 4 Schematic model illustrating proposed hemispheric activation in the Caloric+RIV condition. The perceptual switching in binocular rivalry (RIV) is proposed to activate the right hemisphere (grey circle). Hemispheric activations following caloric stimulation are shown by the red circle following warm irrigations or by blue circles following cold irrigations. The labyrinth represents the side of the caloric irrigation. The size of the circles illustrates the relative degree of the activation. **A** In the RIGHTCOLD+RIV condition, the hemispheres are in conflict, however the right hemisphere exerts a predominant effect (as shown by the relative thickness of the arrows). The interhemispheric conflict

is not present during the RIGHTWARM + RIV condition as the right hemisphere is preferentially activated by both the visual and vestibular stimuli. **B** Similarly, no conflict is present in LEFTCOLD + RIV condition whereas during the LEFTWARM+RIV condition conflict presents, but critically here the left hemisphere exerts a greater influence during the interhemispheric conflict.

Figure 5 Asymmetrical modulation of the VOR during combined caloric irrigation and rivalry viewing. On the y axis we represent the mean % change in peak SPV when comparing the CALORIC alone condition to the corresponding CALORIC+RIV condition. On the x axis we have represented the different conditions, namely cold or warm water irrigations of either the right (dark grey bar) or left (light grey bar) ear. Note that we observe a marked suppression of the VOR for the following conditions, RIGHTCOLD+RIV compared to RIGHTCOLD irrigations alone and LEFTWARM+RIV compare to LEFTWARM irrigations alone. No suppression of the VOR was observed when comparing LEFTCOLD+RIV to LEFTCOLD irrigations alone or RIGHTWARM+RIV to RIGHTWARM irrigations alone. Data marked *** is significant at p<0.001. Error bars indicate standard error.

Figure 6 Probing the neural correlates of the asymmetrical VOR modulation following combined CALORIC+RIV stimulation using tDCS. **A** Top panel represents the results from the cold water irrigations (i.e. group1). On the y axis we represent the mean % change in peak SPV when comparing the CALORIC alone condition to the corresponding CALORIC+RIV condition. On the x axis we have represented the different conditions of either the right (dark grey bar) or left (light grey bar) ear cold water irrigations following either unipolar left anodal, left cathodal, right anodal or right cathodal stimulation. Note that for RIGHTCOLD+RIV we only observed asymmetries of the VOR following either unipolar right hemisphere anodal stimulation and unipolar left hemisphere cathodal stimulation. Note that the asymmetries in the VOR during RIGHTCOLD+RIV were attenuated following either unipolar anodal stimulation of the left hemisphere or unipolar cathodal stimulation of the right hemisphere. **B** Lower panel represents the results from the warm water irrigations (i.e. group 2). Again on the y axis we represent the mean % change in peak SPV when comparing the CALORIC alone condition to the corresponding CALORIC+RIV condition. On the x axis we have represented the different conditions of either the right (dark grey bar) or left (light grey bar) ear warm water irrigations following either unipolar left anodal, left cathodal, right anodal or right cathodal stimulation. Note that for LEFTWARM+RIV we only observed asymmetries of the VOR following either unipolar left hemisphere anodal stimulation or unipolar right hemisphere cathodal stimulation. Note that the asymmetries in the VOR during LEFTWARM+RIV were attenuated following either unipolar anodal stimulation of the right hemisphere or unipolar cathodal stimulation of the left hemisphere. Data marked ** is significant at p < 0.01. Error bars indicate standard errors.

Figure 7 Relationship between numerical perceptual biases and degree of VOR suppression. **A** On the x axis we present the degree of vestibular nystagmus suppression (i.e. % change in SPV) between right cold caloric alone and RIGHTCOLD+RIV. On the y axis we represent the number pair bisection error (%). We observed a significant negative correlation between the number pair bisection error (i.e. bias towards smaller numbers) and the degree of vestibular nystagmus suppression. That is, those individuals who exhibited a larger bias towards smaller numbers during RIGHTCOLD+RIV also demonstrated a larger degree of vestibular nystagmus suppression. **B** On the x axis we present the degree of vestibular nystagmus suppression (i.e. % change in SPV) between left warm caloric alone and LEFTWARM+RIV. On the y axis we represent the number pair bisection error (%).We observed a significant positive correlation between the number pair bisection error (i.e. bias towards larger numbers) and the degree of vestibular nystagmus suppression. That is, those individuals who exhibited a more pronounced bias towards larger numbers demonstrated greater vestibular nystagmus suppression.

Figure 8 Relationship between lateral shifts observed during numerical clock drawings and degree of VOR suppression. On the x axis we represent the degree of vestibular nystagmus suppression and on the y axis we represent the relative shift in the centre of mass (arbitrary units). **A** For RIGHTCOLD+RIV, we observed a positive correlation, in that those individual who exhibited greater VOR asymmetries had larger shifts in the centre of mass to the right. **B** For LEFTWARM+RIV, we also observed a positive correlation, in that those individual who exhibited greater VOR asymmetries had larger shifts in the centre of mass to the left.

Figure 9 Summary of the results for the effects of frontal tDCS upon numerical magnitude allocation. On the y axis we represent the mean change in bisection error (%) when comparing caloric alone to the corresponding CALORIC+RIV condition, either before (dark grey bars) or after (light grey bars) application of tDCS. On the x axis we represent the 4 different tDCS stimulation paradigms implemented. **A** No effect of tDCS upon number pair bisection was observed in any of the 4 stimulation conditions during RIGHTWARM+RIV. **B** For LEFTWARM+RIV, there was a bias towards larger numbers before application of tDCS, which was abolished following either unipolar right anodal and left cathodal stimulation. Notably, this bias towards larger numbers was augmented following either unipolar left anodal or right cathodal stimulation. **C** During RIGHTCOLD+RIV, there was a bias towards smaller numbers before tDCS, however this bias was abolished following either unipolar left anodal stimulation or right cathodal stimulation and augmented following either unipolar right anodal or left cathodal stimulation respectively. **D** No effect of tDCS was observed

upon number pair bisection in any of the 4 stimulation conditions during LEFTCOLD+RIV. Data marked * significant at p< 0.001. Error bars indicate standard errors.

Figure 10 Computational modelling. The figure illustrates the probability distribution *p(x;l,r)* that occurs for several different values of l where the following parameters were implemented in the model *r*=3.0 and β = 1.

Bidirectional modulation of numerical magnitude

Running Title: Control of Number Allocation

SUPPLEMENTAL DATA

Supplemental material 1; Analysis of clock drawings

Two different methods were employed to analyse the clock drawings: Centre of Mass and Number spacing. For illustration purposes only, we performed heat map analysis.

1. Centre of Mass analysis: To analyse the behavioural data from the clock drawing experiment we developed an objective process for measuring the relative horizontal distortion in each image. This was based on the position of the COM of the drawing relative to a reference point. As each clock was drawn starting with the numeral 12, we used the position of the 12 as the internal reference point for each image. Since the clock drawings differed between individuals, we compared the position of the COM of the whole drawing relative to the position of the reference point with respect to the size of the image canvas. This ensured that the position of the COM of the drawing could be calculated as a fraction of the size of the image canvas for each clock, providing a scale invariant measure of distortion for each participant. There were two critical steps in pre-processing the images. First, the 12 was aligned with the horizontal midpoint of the *image canvas.* This was achieved by calculating the COM of the 12, and then shifting the drawing laterally on the canvas such that it was aligned with the horizontal midpoint of the image canvas. The image canvas was then cropped so that the most lateral element of the drawing was within 2 pixels of the edge of the image canvas. We then calculated shifts in the COM of the drawing relative to the size of the image canvas, thus providing a scale invariant index of the position of the COM of the drawing relative to the 12. This relative distortion approach enabled within-subject comparisons to be made for the different stimulation conditions irrespective of the physical size of the clocks and was developed to be sensitive to horizontal shifts in COM. All data were digitised using a high resolution flatbed scanner (Epson 1650, 1600 dpi) and then processed using MATLAB (Mathworks) version 7.14.0.739 (R2012a). The COM was calculated using code adapted from the MATLAB file exchange (centerOfMass.m, author: Jered Wells, Duke University).

2. *Number spacing analysis*: We also explored the average spacing of numbers on the right and left sides of the clock faces. The images were prepared as described in the centre of mass analysis, and then the X and Y coordinates of the centre of mass for each number character were calculated. This was then used to generate the distance between adjacent numbers for each clock. The mean spacing between the numbers on the right side of the clock face (12->6) and those on the left hand side of clock face (6->12) was calculated and normalised by the mean separation between all characters in the clock face. Hence a single value for each clock side was produced

and a ratio of the separation between numbers on the right and the numbers on the left was calculated. A ratio of >1 suggests an average expansion of spacing between numbers on the right side of the clock or contraction of spacing between numbers on the left side.

Heat map Analysis: To graphically illustrate the lateral shifts observed in the 'Caloric+RIV' conditions we used a 'heat mapping' technique to display these shifts for each condition (Fig. S1). We specifically were interested in comparing the relative position of the numbers in each clock and how they were spatially distributed. In addition to the pre-processing steps taken for the COM analysis, the images were transformed into a standard space such that the distance in pixels between numerals 12 and 6 was identical for all the drawings collected. This step enabled images for multiple participants to be overlapped for each condition. The images were then convolved with a 2D Gaussian kernel, generated using code adapted from the Matlab file exchange (file exchange "customgauss", author: Thomas Diederiksen). The individual heat maps were then binarised and summated for all participants for each condition. A maximum value of 10 was given where there was maximal overlap, or 0 for no overlap between participants (Fig. S1).
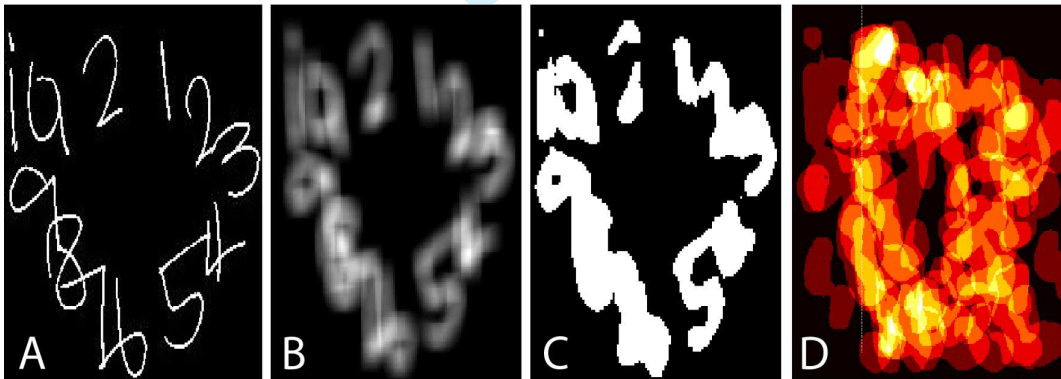
Figure S1; Each clock was processed prior to combining to generate heat maps for each condition. (A) Raw imported image. (B) Image convolved with 2D Gaussian. (C) Binarised image following convolution. (D) Group overlap image (n=10).

Supplemental material 2; Representative example of numerical clock drawings
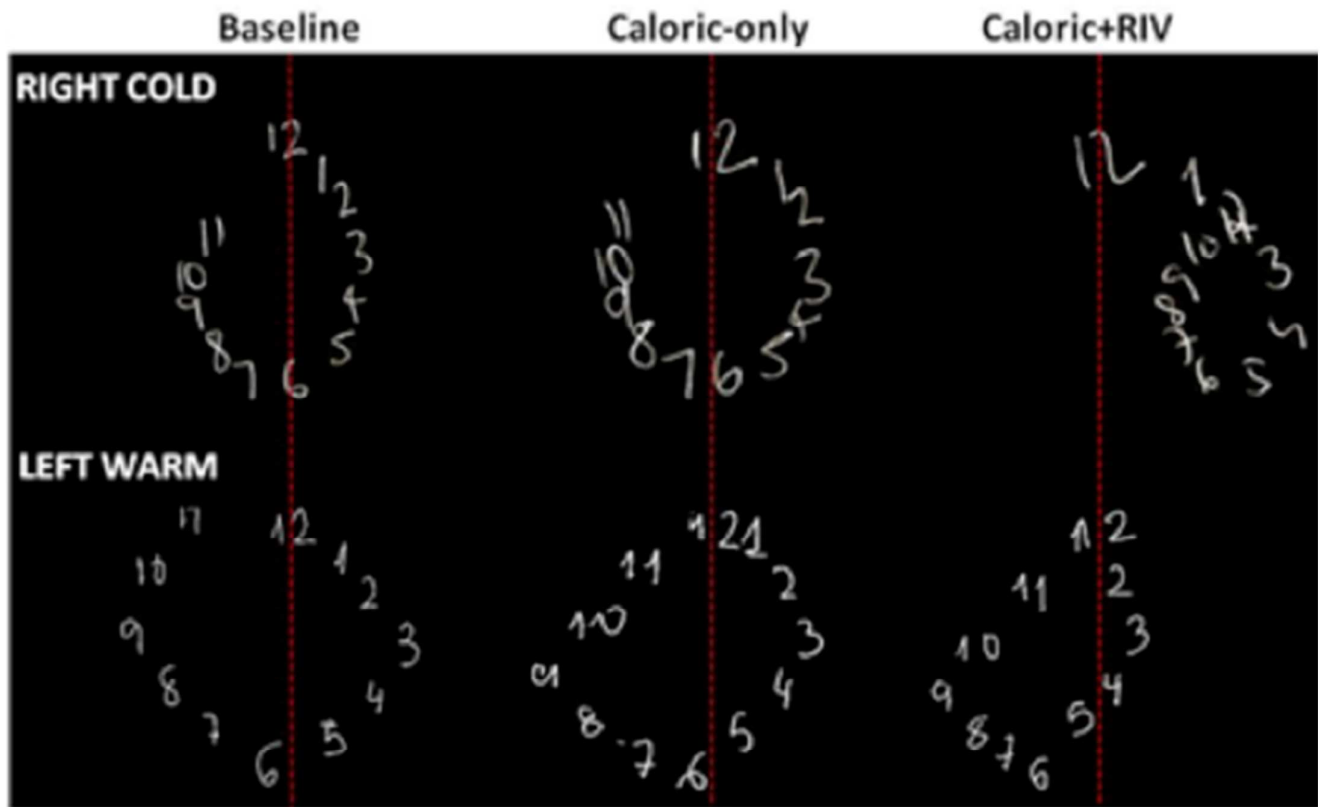

Figure S2; Representative numerical clock drawings from a single subject. Upper panel shows the drawings for the baseline condition (i.e. no stimulation /darkness), following RIGHTCOLD caroric only and RIGHTCOLD+RIV all drawn _clockwise._ Note the rightward lateral displacement of the numerical clock drawing following RIGHTCOLD+RIV. Lower panel shows the drawings for the for the baseline condition (darkness, no stimulation), following LEFTWARM caloric only and LEFTWARM+RIV all drawn _anti-clockwise_. Note the leftward lateral displacement of the numerical clock drawing following LEFTWARM+RIV

Supplemental material 3; Physiological manipulation of numerical magnitude using a visuo-spatial working memory task and vestibular stimulation

Previous reports have demonstrated that vestibular activation alters the switching rate of alternate percepts during the experience of binocular rivalry (Miller et al. 2000). To demonstrate that the effects reported in the main experiments were not specific to binocular rivalry per se, but rather secondary to a generalised involvement of visuospatial processing resources in a right lateralised fronto-parietal attention network (Knapen et al. 2011; Lumer, Friston, Rees 1998; Paffen and Van der Stigchel 2010; Sterzer, Kleinschmidt, Rees 2009) we substituted the rivalry component of the stimulation paradigm with a visuospatial working memory task (VST) (Brooks 1967; Corbetta and Shulman 2002),which we have previously employed and shown to have comparable effects (Arshad, Nigmatullina, Bronstein 2013). This consisted of a modified Brooks visuospatial paradigm where numbers were substituted with shapes (Brooks 1967). Subjects were verbally presented and required to visually imagine a 3X3 grid and 6 shapes (e.g. circle, rectangle, and triangle) that were randomly allocated to a grid position. The subject's task was to remember the shape and its allotted position in the grid. After the task the subjects were required to recall the shapes and their respective position. The minimum criterion set was 4 correct shapes in the allotted positions out of a total of 6 (Arshad et al. 2013; Brooks 1967).

A total of 20 right-handed subjects participated (Handedness score over 40) (Oldfield 1971) (12 female, age range 18-24 years, mean age 22 years). 10 subjects participated in cold and 10 subjects in warm water irrigations. All subjects were naive to purpose of study had no history of otological, ophthalmological, psychiatric or neurological disorders and provided written informed consent as approved by the local ethics research committee.

No effect of performing the VST alone was observed upon numerical judgements [VST vs no VST: $p > 0.05$, $F_{(2,18)} = 0.10$, Repeated Measures ANOVA]. During combined stimulation (See Figure S3), repeated measures ANOVA (3x2x2) [within-subjects factors: condition; 3 levels (BASELINE, CALORIC, CALORIC+VST), side of caloric stimulation; 2 levels (right, left ear) and temperature of caloric stimulation; 2 levels (warm, cold)] revealed that both the temperature of caloric and side of caloric stimulation showed significant main effects [$p < 0.01$, $F_{(1,9)} = 13.4$ and $p < 0.05$, $F_{(1,9)} = 9.73$ respectively]. The following interactions were significant: temperature*side of stimulation, temperature*condition and side of

stimulation*condition [p < 0.001, F (1,9) = 42.2; p = 0.023, F (2,18) = 5.01; p = 0.005, F (2,18) = 8.08 respectively]. Post-hoc paired t-tests showed no significant difference (all p > 0.05) between baseline and caloric-only conditions. Post-hoc paired t-tests with Bonferroni corrections between caloric-only and CALORIC+VST showed significant differences only for RIGHTCOLD+VST (bias towards smaller numbers) (Fig. S3A) and LEFTWARM+VST (bias towards larger numbers) [p = 0.004, t = 5.12; p = 0.012, t = 3.98 respectively] (Fig. S3B). No significant differences were observed for either LEFTCOLD+VST or RIGHTWARM+VST (p > 0.05) (Fig; S3A and S3B).
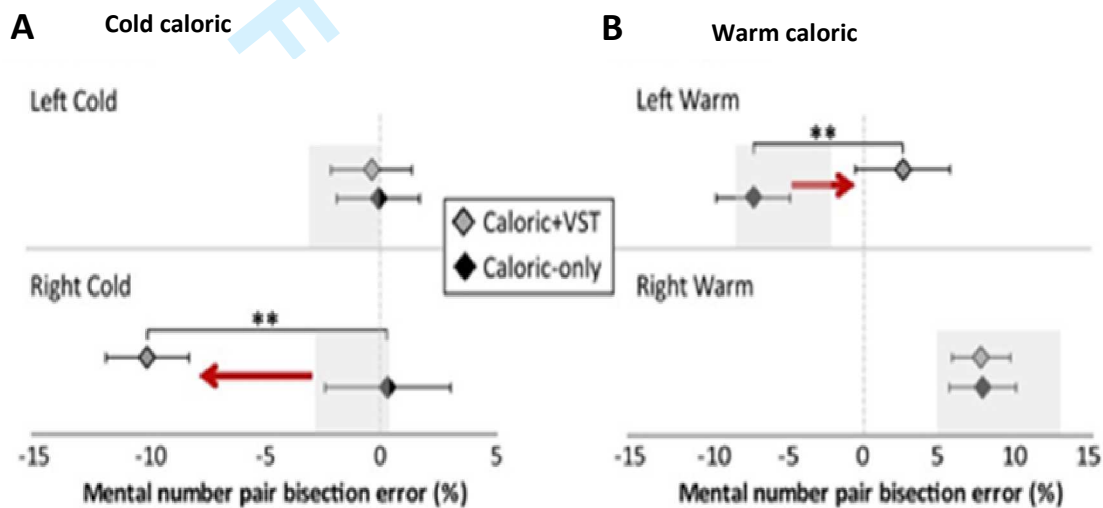
Figure S3 Results from mental number pair bisection experiments following physiological manipulations. We present the mean % bisection error from the midpoint of the numerical interval. (A) 'Caloric+VST' condition (grey diamonds) resulted in subjects significantly underestimating the midpoint (i.e. shift to the left as indicated by red arrow) when compared to 'Caloric-only' (black diamonds) condition following RIGHTCOLD+VST (lower left hand side panel), but no effect was found during LEFTCOLD+VST (upper left hand side panel). (B) In contrast, following LEFTWARM+VST (upper right hand side panel) the subjects showed significant shift towards larger numbers (i.e. rightward shift as indicated by red arrow), suggesting overestimation of the midpoint (upper panel). No effect of RIGHTWARM+VST was observed (lower right hand side panel). Grey shaded area in panels indicates 95% confidence limits calculated from baseline measures (i.e. no caloric or vestibular stimulation). Dashed line at 0 corresponds 0% error i.e. accurate bisection. Data marked ** is significant at p < 0.01; data marked * is significant at p < 0.05. Error bars indicate standard errors.

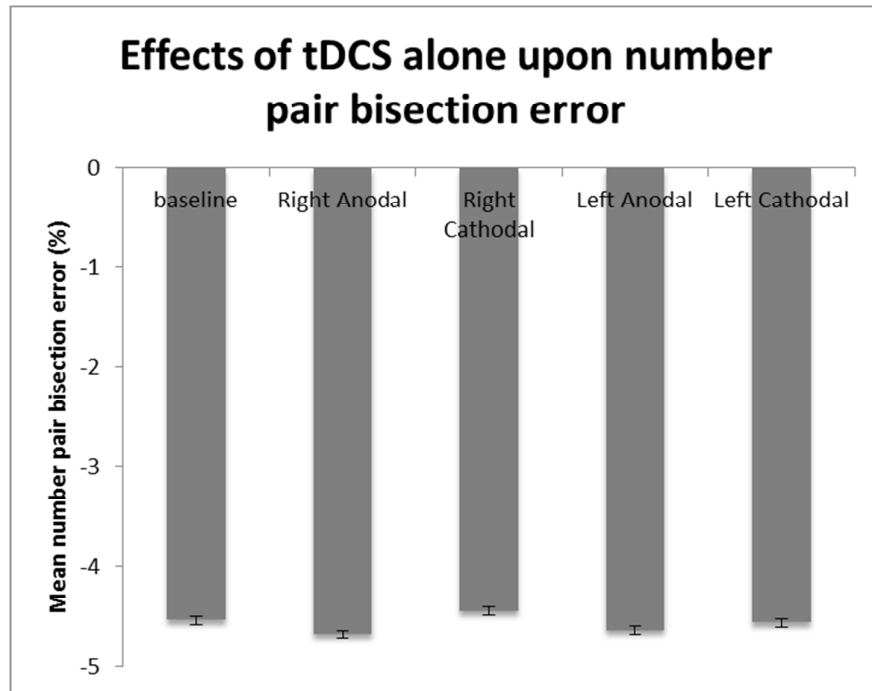**Supplemental material 4; Effects of tDCS alone upon number pair bisection**

Figure S4 Results from mental number pair bisection task following application of unipolar frontal tDCS alone. On the x axis we represent the 5 different conditions. On the y axis we represent the mean number pair bisection error (%). As shown, none of the four tDCS conditions (i.e. right anodal, right cathodal, left anodal or left cathodal) modulated the numerical responses compared to the baseline. Error bars indicate standard error.

Supplemental material 5; Analysis of inter-digit spacing during clock drawings

 For the numerical clock drawings we performed the inter digit spacing analysis as described above for all caloric only conditions and CALORIC+RIV conditions. As shown in Figure S4 below, the inter-digit spacing falls outside the 95% confidence intervals only for RIGHTCOLD+RIV and LEFTWARM+RIV conditions. Following RIGHTCOLD+RIV we observed an expansion for smaller numbers (blue circles) and compression for larger numbers (red squares). Following the LEFTWARM+RIV condition we observed compression for small numbers (blue circle) and expansion of larger numbers (red squares). To ascertain whether these changes in inter-digit spacing were related to hand dominance we correlated each individual's handedness score as determined by the Edinburgh handedness inventory questionnaire with individual differences in inter-digit spacing. For RIGHTCOLD+RIV, we observed no correlation between handedness and expansion between smaller numbers (R^2 0.014 p > 0.05 Pearson's correlation) nor for compression between larger numbers (R^2 0.037 p > 0.05 Pearson's correlation). For LEFTWARM+RIV, we observed no correlation between handedness and expansion between large numbers (R^2 0.124 p > 0.05 Pearson's correlation) nor the compression between smaller numbers (R^2 0.0758 p > 0.05 Pearson's correlation).
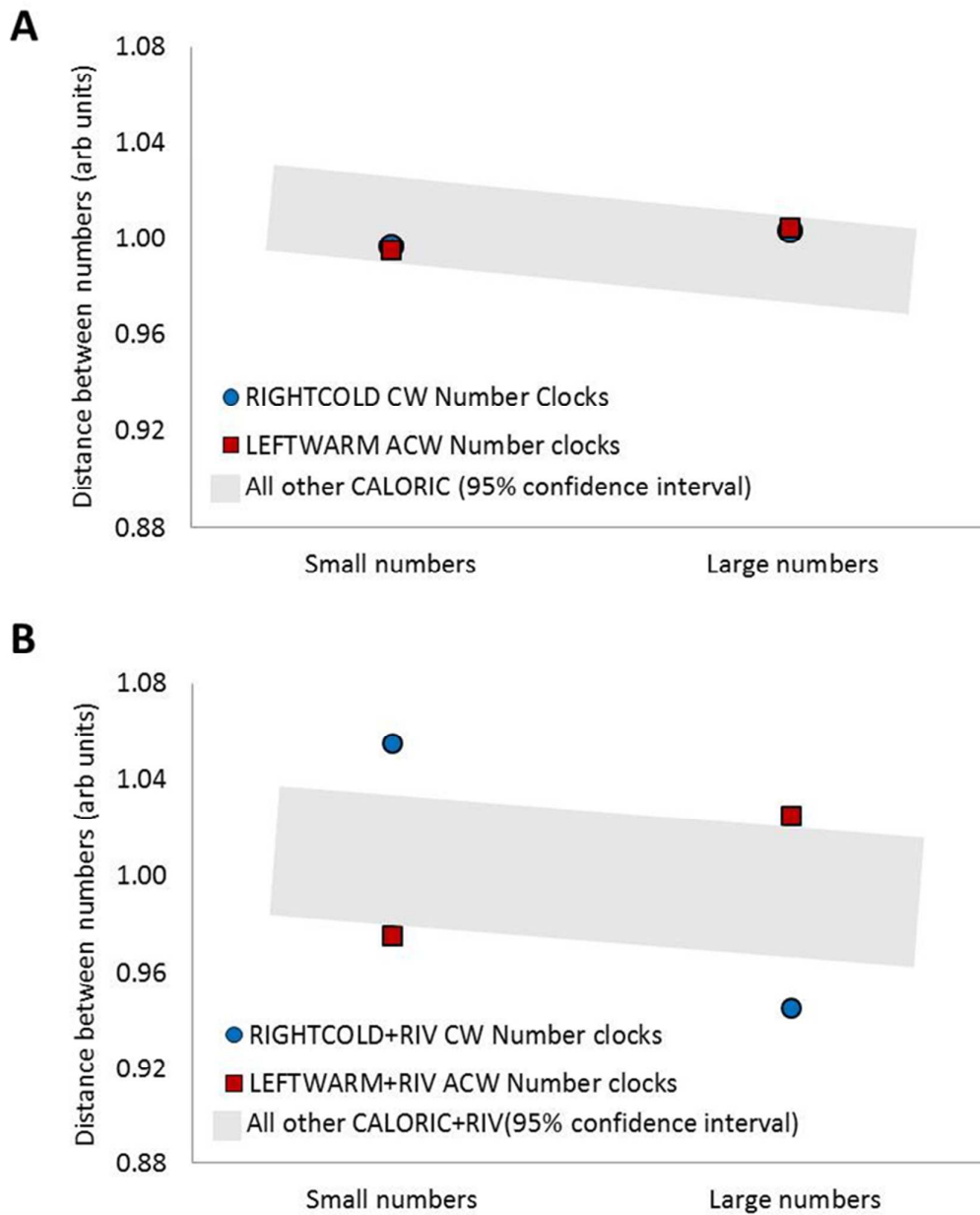
Figure S5 Showing inter digit spacing for all the numerical clocks drawn during the caloric only conditions (A) and CALORIC+RIV conditions (B). Grey shaded area in both panels indicates 95% confidence limits with respect to the distance between numbers. In (A) the distance between numbers for both right cold caloric (blue circle) and left warm caloric (red square) alone, which as shown falls within the 95% confidence intervals. As shown in (B), the inter-digit spacing falls outside the 95% confidence intervals only for RIGHTCOLD+RIV (blue circles show for expansion for smaller and compression for larger numbers) and LEFTWARM+RIV (red squares show compression for small numbers and expansion of larger numbers) conditions.

Supplemental material 6; Verification of the computational model by applying it to the SNARC effect

Verification of our computational model is provided by applying it to the SNARC effect. The SNARC effect demonstrates that subjects respond quicker with the right hand if the number is larger than the reference and quicker with the left hand if the number is smaller than the reference (Dehaene, Bossini, Giraux 1993). It is proposed that larger/left and smaller/right are conflicting pathways whereas smaller/left and larger/right do not introduce conflict. More errors are made if the task involves a conflicting pathway which can be modelled as follows. Let $p_<$ and $p_>$ be the probabilities that the subject produces the answer that corresponds to the presented number being smaller and, respectively, larger than the reference. Let s_1 be the variable denoting the state of the response; $s_1 = 1$ response is "greater" and $s_1 = -1$ response is "smaller". Let s_2 be the variable denoting the nature of the task; $s_2 = 1$ respond with right hand and $s_2 = -1$ respond with left hand. The appropriate energy function for the SNARC experiments is;

$$E(s_1, s_2, J, h) = -hs_1 - Jhs_1s_2, \quad [1]$$

where $h > 0$ and $J > 0$.

The probabilities are given by the Boltzmann distribution:

$$p_>(s_2, J, h) = \frac{\exp\big(E(1, s_2, J, h)\big)}{\exp\big(E(1, s_2, J, h)\big) + \exp\big(E(-1, s_2, J, h)\big)} \quad [2]$$

$$p_<(s_2, J, h) = \frac{\exp\big(E(-1, s_2, J, h)\big)}{\exp\big(E(1, s_2, J, h)\big) + \exp\big(E(-1, s_2, J, h)\big)} \quad [3]$$

Parameter h denotes the magnitude of the difference between the presented and the reference number. If the two numbers are equal, $h = 0$, and the response is equally likely to be either "larger" or "smaller". Parameter J denotes the strength of the conflict.

The first term in equation [1] simply states that increasing the difference between the given number and the reference number increases the probability of the right answer. The second term in equation [2] is the conflict term implemented to reduce the probability of the right answer if the task contains a conflict and to increase the probability of the right answer in the case of a non-conflict task. Figure S5 shows the plot of the function $p_>$ as a function of hs_1 for three different values of Js_2. Thus the SNARC effect and our model can be explained by the conflict term $-Jhs_1s_2$ of the energy function [1].
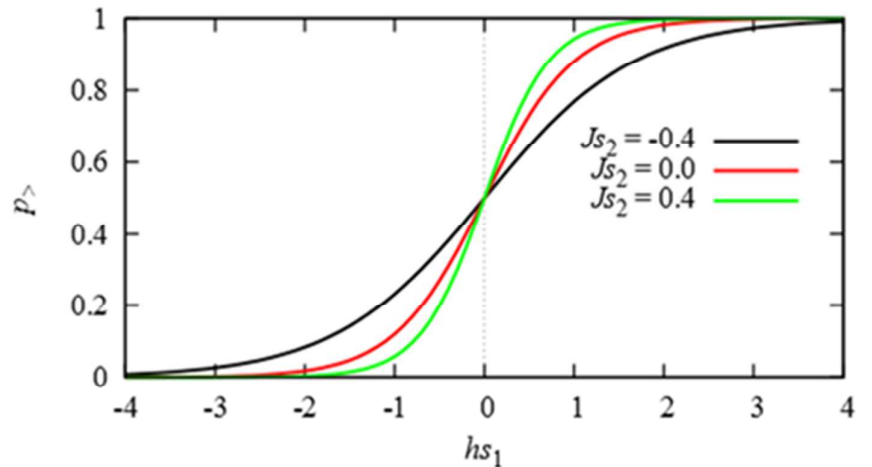
Figure S6; Computational modelling. Here, we apply the model to predict the SNARC effect specifically the aspect of providing the answer "greater" than the midpoint as a function of the difference between the given number and the reference number for three different conditions. The curve of $Js_2 = 0$ is a control i.e. a curve representing no conflict, for example, when the subject is asked to verbally respond to the magnitude comparison task rather than with a hand. We can observe that when $s_2 < 0$ (the subject has to respond with the left hand), then the probability of the right answer, when the given number is greater decreases, and when the given number is smaller increases. Conversely, when $s_2 > 0$ (the subject has to respond with the right hand), then the probability of the right answer when the given number is greater increases, and when the given number is smaller decreases.

Supplemental material 7; Straight ahead pointing experiment

In order to directly ascertain whether the observed modulation in the visuo-motor transformations were attributable solely to a numerical bias and not a spatially lateralised motor bias we performed a straight-ahead pointing experiment. The protocol was adapted from a study that examined the relationship between subjective straight-ahead and long line bisection in neglect patients. 10 new right handed healthy subjects (7 males /3 females; age range 20-30, mean age 24 years) were recruited. The same experimental set-up was used as the one for visuo-motor transformation task. An A2 sized drawing board fixed with white A3 paper was placed on the lap against the subject's knees. In the baseline condition (darkness), subjects were asked to raise their right hand, holding the pen, so that the experimenter could guide the pen to the 'start' point on the marked A3 paper by holding the pen without touching the subject's hands. Subjects were then instructed to mark a new point straight ahead, approximately 30cm from the start point. This mark was taken as their subjective straight ahead (SSA) (Richard et al. 2004). This was performed for both caloric-only and Caloric+RIV conditions. In each of the conditions, both left and right ear irrigations with cold and warm caloric irrigations were performed in a randomized order. Five trials were carried out in each condition. No significance for factor 'side' (p>0.05, F=2.26,df=1) nor for condition (p>0.05, F=3.08,df=2) was observed, with either cold or warm caloric alone compared to the corresponding CALORIC+RIV condition.

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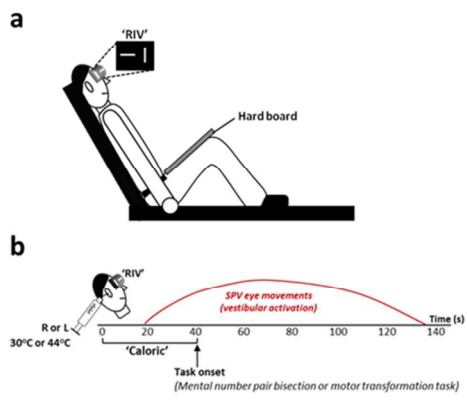47
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Figure 1

a

'RIV'

Hard board

b

'RIV'

SPV eye movements
(vestibular activation)

Time (s)

R or L
30°C or 44°C

0   20   40   60   80   100   120   140

'Caloric'

Task onset
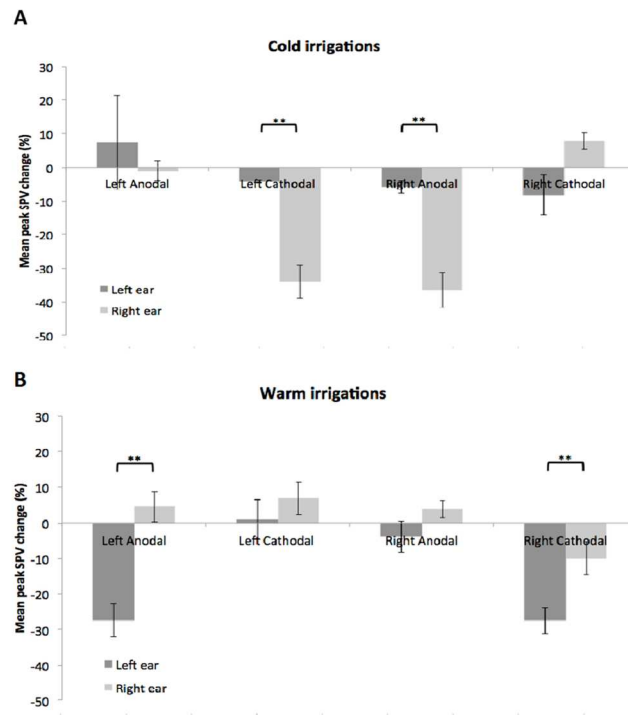(Mental number pair bisection or motor transformation task)

Figure 1
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Figure 2
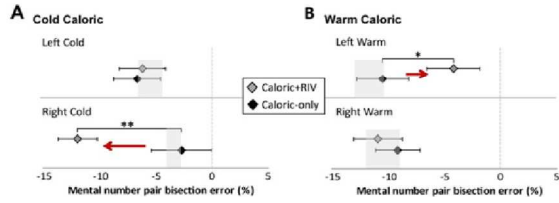
Figure 2
209x297mm (150 x 150 DPI)

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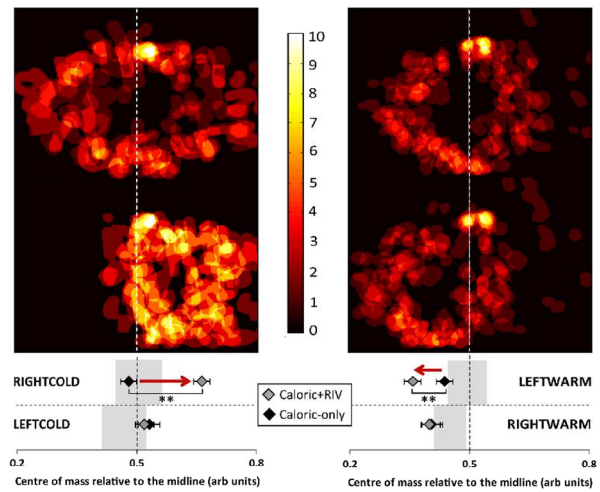
Figure 3
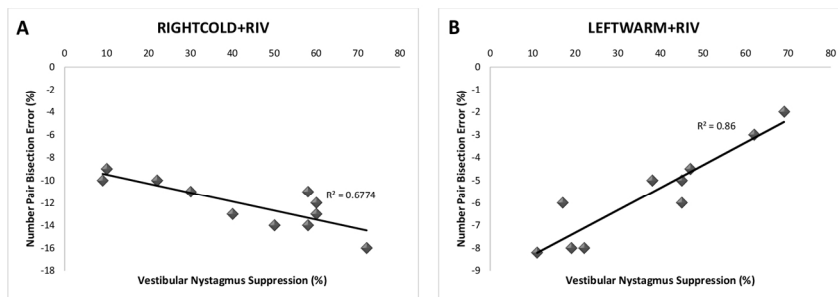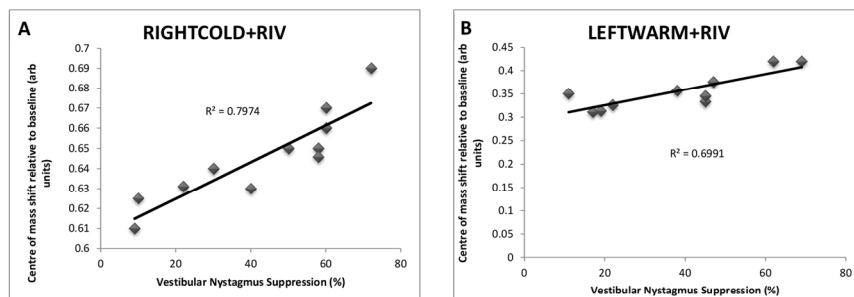209x297mm (150 x 150 DPI)
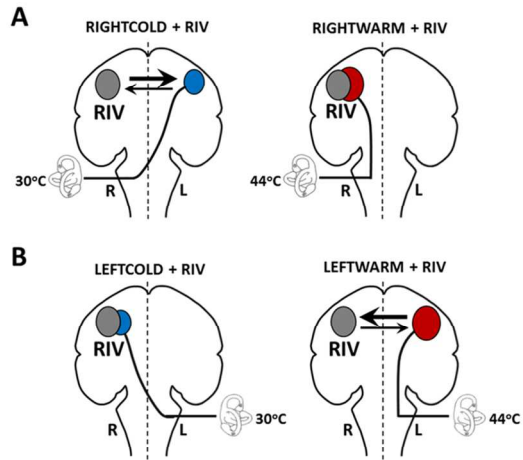
Figure 4
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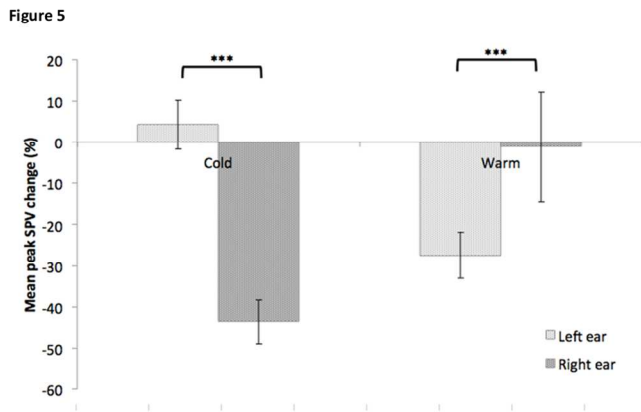
Figure 5
209x297mm (150 x 150 DPI)

Figure 6
209x297mm (150 x 150 DPI)

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Figure 7

Figure 7
297x209mm (150 x 150 DPI)

Figure 8
297x209mm (150 x 150 DPI)

Figure 9
297x209mm (150 x 150 DPI)

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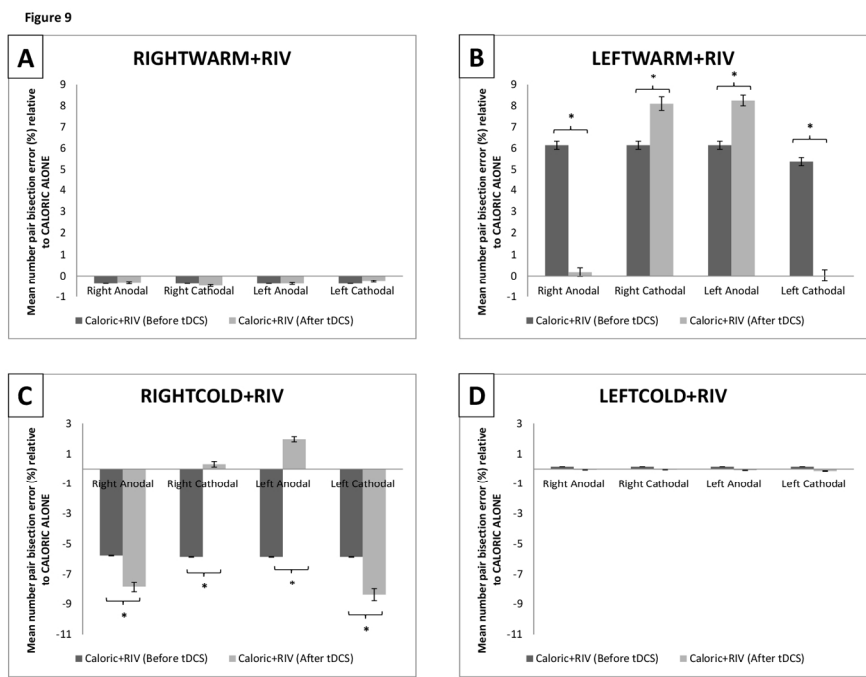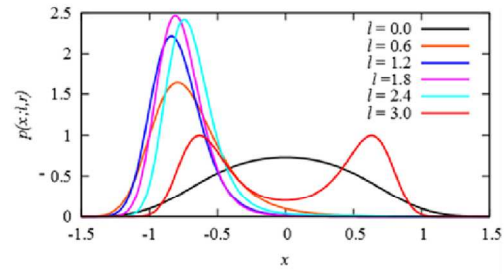42
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Figure 10

Figure 10
209x297mm (150 x 150 DPI)