Somatotopy and temporal dynamics of sensorimotor interactions: evidence from double afferent inhibition

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Abstract

Moving and interacting with the world requires that the sensory and motor systems share information, but while some information about tactile events is preserved during sensorimotor transfer the spatial specificity of this information is unknown. Afferent inhibition studies, in which corticospinal excitability is inhibited when a single tactile stimulus is presented before a transcranial magnetic stimulation pulse over the motor cortex, offer contradictory results regarding the sensory-to-motor transfer of spatial information. Here, we combined the techniques of afferent inhibition and tactile repetition suppression (RS: the decreased neurophysiological response following double stimulation of the same vs. different fingers) to investigate whether topographic information is preserved in the sensory-to-motor transfer in humans. We developed a double afferent inhibition paradigm to examine both spatial (same vs. different finger) and temporal (short vs. long delay) aspects of sensorimotor interactions. Two consecutive electrocutaneous stimuli (separated by either 30 or 125 ms) were delivered to either the same or different fingers on the left hand (i.e., index finger stimulated twice or middle finger stimulated before index finger). Information about which fingers were stimulated was reflected in the size of the motor responses in a time-constrained manner: corticospinal excitability was modulated differently by same and different finger stimulation only when the two stimuli were separated by the short delay (p=.004). We demonstrate that the well-known response of the somatosensory cortices following repetitive stimulation is mirrored in the motor cortex and that corticospinal excitability is modulated as a function of the temporal and spatial relationship between afferent stimuli.

Introduction

In order to sensibly interact with the world and skilfully manipulate objects information needs to be shared between the somatosensory and motor systems (Rossi *et al.*, 1998; Brochier *et al.*, 1999; Nelson *et al.*, 2004). The two systems communicate via a network of extensive connections between the sensory and motor cortices (Asanuma *et al.*, 1968; Strick & Preston, 1978; Stepniewska *et al.*, 1993; Andersson, 1995; Huffman & Krubitzer, 2001; Makris *et al.*, 2005; Shinoura *et al.*, 2005; Eickhoff *et al.*, 2010; Mao *et al.*, 2011; Catani *et al.*, 2012), but also by motor cortex cells responding directly to sensory stimuli (Albe-Fessard & Liebeskind, 1966; Goldring & Ratcheson, 1972; Fetz *et al.*, 1980; Fromm *et al.*, 1984) and sensory cortex cells controlling motor behaviour (Matyas *et al.*, 2010). Despite having relatively good knowledge of the anatomical substrate for communication between the primary sensory and motor cortices, particularly with respect to the hand (Hikosaka *et al.*, 1985), our understanding of what information is transferred remains poor.

It is well known that the excitability of the sensory system is reduced when two afferent stimuli separated by an appropriate delay are delivered to the same location (McLaughlin & Kelly, 1993; Ragert *et al.*, 2008; Wühle *et al.*, 2011; Lenz *et al.*, 2012; Young-Bernier *et al.*, 2012; Gatica Tossi *et al.*, 2013). In recent studies using this repetition suppression (RS) paradigm we showed stronger RS (i.e. less activity) in the primary somatosensory cortex (SI) when the same finger was stimulated twice than when two adjacent fingers were stimulated (Tamè *et al.*, 2012, 2014), suggesting that SI responds in a finger-specific manner. On the basis of this finding we reasoned that if somatic topology is preserved in the transfer from the somatosensory to the motor cortices, then the activity of the motor cortex should be different after index-index than middle-index cutaneous stimulation. To investigate this we took the typical afferent inhibition (AI) protocol in which a single cutaneous stimulus delivered at an appropriate delay reduces the amplitude of the

muscular response evoked by transcranial magnetic stimulation (TMS) (Delwaide & Olivier, 1990; Chen *et al.*, 1999; Tokimura *et al.*, 2000; Abbruzzese *et al.*, 2001; Miniussi *et al.*, 2013) and modified it to include the presentation of two stimuli either at the same or different locations.

The specific aim of the present work was to combine the RS and AI approaches to investigate whether the somatic topology of the somatosensory response to two stimuli is transferred to the motor cortex. Specifically, we investigated whether spatial information about which fingers are stimulated (index-index or middle-index) is reflected in the excitability of the motor cortex, or whether the output of the motor system does not preserve information about their spatial distribution. To test this hypothesis we modified the afferent inhibition paradigm (Tamburin *et al.*, 2005) by delivering two tactile stimuli (same or different fingers) separated by a short (30 ms) or long (125 ms) delay at various times before a single TMS pulse over the contralateral motor cortex.

Material and Methods

Participants

Seventeen healthy subjects (mean age = 27 years, SD = 6; range 20-44 years; 10 females) took part in the experiment after giving written informed consent and being screened for contraindications to TMS. Fourteen were right-handed by self-report, and all reported normal somatosensation and were not aware of the specific purpose of the study. The study was approved by the local ethics committee and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki (last update: Seoul, 2008).

Experimental Setup

During the experiment participants were comfortably seated in front of a computer screen

with both hands resting on their thighs in a palm-up position. Vision of their hands was occluded by a black cloth positioned over the forearms and hands. To examine cortical excitability following same versus different finger stimulation two consecutive electrocutaneous stimuli (adaptor and probe) were delivered to either one or two fingers on the left hand. This is very similar to the approach adopted by the classical short- (Delwaide & Olivier, 1990; Tokimura *et al.*, 2000) and long- (Chen *et al.*, 1999; Abbruzzese *et al.*, 2001) latency afferent inhibition studies that with single afferent touch investigated corticospinal excitability (CSE) reflecting sensorimotor integration. The two stimuli on these double afferent stimulation trials were separated by either a short (30 ms) or long (125 ms) delay, and the first stimulus was delivered to either the index or middle finger (adaptor) whereas the second was always delivered to the index finger (probe) (i.e., short/long$_{\text{index-index}}$ and short/long$_{\text{middle-index}}$; Figure 1). We limited our protocol to conditions in which the index finger was the second stimulated finger due to time constraints and because the majority of afferent inhibition studies examine index finger stimulation.

The 30 and 125 ms delays were chosen because the somatosensory activation within SI is assumed to persist for at least 60 ms (Allison *et al.*, 1992; Mauguière *et al.*, 1997) and its signal recovery time has been reported to be about 110 ms (Hamada *et al.*, 2002). Thus, in the 30 ms condition the processing of both stimuli overlapped within SI (Chung *et al.*, 2002; Martin-Cortecero & Nuñez, 2014; Nakagawa *et al.*, 2014), whereas in the 125ms condition the first stimulus is processed by SI before the second stimulus arrives and therefore the stimuli interact at later stages, most likely in SII or the parietal cortex. The rationale behind these specific timings comes from the different retention time of the somatosensory signal in SI. This argument has been recently confirmed in a study from our group using magnetoencephalography (MEG) in which we demonstrated that two afferent stimuli applied to the fingers interact differently in the somatosensory cortices when separated by 30 or 125 ms (Tamè *et al.*, 2014).

The second afferent stimulus was always applied to the index finger and was followed by a single TMS pulse over the right motor cortex at one of five possible inter-stimulus intervals (ISIs) (15, 30, 45, 60, or 75 ms) (see Figure 1). These ISIs are similar to those used in a number of previous studies investigating short afferent inhibition (Tokimura *et al.*, 2000; Helmich *et al.*, 2005; Tamburin *et al.*, 2005). To determine if two consecutive afferent stimuli modulated CSE we compared CSE on double afferent stimulation trials with CSE on single afferent stimulation trials on which a single stimulus was delivered to the index finger followed by a single TMS pulse at one of the same five ISIs used for the double afferent stimulation trials (15, 30, 45, 60, or 75 ms). Note that we use the term DELAY to refer to the temporal interval between two cutaneous afferent stimuli (delay = 30 or 125 ms) and the term inter-stimulus interval (ISI) to refer to the temporal interval between the second afferent stimulus and the TMS pulse on double afferent stimulation trials and between the single afferent stimulus and the TMS pulse on single afferent stimulation trials (ISI = 15, 30, 45, 60, or 75 ms).

<Please insert Figure 1 about here>

Cutaneous stimulation

Tactile stimulation consisted of a brief (100 μs) single electrical pulse delivered by a constant current stimulator (DS7A, Digitimer Ltd, UK). To ensure that the stimulated area was limited to the volar surface of the distal phalanges of each finger we used bipolar adhesive electrodes which were placed on the distal and middle phalanges of the left index and middle fingers with the anode approximately 2 cm proximal to the cathode. Prior to commencing the TMS phase of the experiment the sensory threshold - the minimal stimulus intensity detectable by the participant on five out of ten trials - was determined for each finger separately using a staircase

procedure. The intensity of the tactile stimulus used throughout the experiment was set at 2.5 times the sensory threshold. The choice of this particular intensity was dictated by the results of a previous study showing that lower intensities did not always induce SAI and that inhibition produced by higher intensities was not modulated by the interval between the tactile stimulus and the TMS pulse (Tamburin *et al.*, 2001; Wood *et al.*, 2010).

Physiological Measurements and Transcranial Magnetic Stimulation

Electromyographic (EMG) activity was recorded using Ag-AgCl surface electrodes placed over the first dorsal interosseus (FDI) of the left hand. FDI was chosen because there is an extensive body of literature examining the effect of cutaneous stimulation of the index fingertip on TMS-evoked responses in this muscle (Tokimura *et al.*, 2000; Helmich *et al.*, 2005; Tamburin *et al.*, 2005; Bikmullina *et al.*, 2009). The EMG signal was sampled at 2000 kHz, digitalised using an analogue-to-digital converter (Power 1401II, Cambridge Electronics Design, Cambridge, UK) and stored on a computer for off-line data analysis.

MEPs were evoked using a Magstim 200 stimulator with a 70 mm diameter figure of eight coil (Magstim. Company, Carmarthenshire, UK) positioned over the right M1 with the handle pointing backwards at an angle of approximately 45° to the sagittal plane. The optimal scalp position for stimulating FDI was marked on a close-fitting cap placed on the participant's head, and the stimulator intensity chosen was the intensity that elicited MEPs of approximately 1 mV in FDI.

Procedure

Each experimental trial started with a black cross on a grey background displayed in the centre of the screen. Participants were asked to fixate the cross during the experimental session.

At a random delay between 0 and 500 ms after the cross was displayed participants received either one or two tactile stimuli followed by a TMS pulse or a TMS pulse alone. Every 29 trials participants were invited to take a short break and the experimenter verified that the TMS coil was correctly positioned. A total of 384 trials [12 for each tactile-TMS trial-type (6) and ISI (5) plus 24 TMS-only trials] were delivered in a totally randomized design. TMS-only trials were equally distributed in each quartile of the testing session. Inter-trial intervals ranged between 5 and 6 seconds. The whole experiment, including the time to establish the TMS and cutaneous stimulation parameters, lasted approximately two hours.

Analysis

The peak-to-peak MEP amplitude between 15 and 50 ms after the TMS pulse was calculated using a custom-written Spike 2 script. To calculate the percentage of inhibition induced by the presence of two rather than one tactile stimuli the average peak-to-peak MEP amplitude recorded on double tactile stimulation trials (i.e., middle-index and index-index) was normalised to the average peak-to-peak MEP amplitude recorded on single (index) tactile stimulation trials. Thus, a value of 33% corresponds to a MEP on a double afferent trial one-third the size of the MEP evoked after index finger stimulation alone.

The standard technique for analysing modulations of tactile repetition suppression by finger identity (same vs. different between adaptor and probe) is to compare the physiological signal during double same-finger versus double different-finger trials (see Wühle *et al.*, 2010; Li Hegner *et al.*, 2007, 2010; Tamè *et al.*, 2012). Thus we performed a three-way repeated measure ANOVA on the amplitude of the normalised double stimulation MEPs with CONDITION (same fingers, different fingers), DELAY (30 and 125) and TOUCH-TMS ISI (15, 30, 45, 60, 75) as within-participant

factors. All data passed the Kolmogorov-Smirnov and Shapiro-Wilk tests for normality. Two-tailored paired *t*-tests were used for all planned comparisons.

Results

The standard analysis technique in afferent inhibition studies is to examine changes in corticospinal excitability in the presence of a single afferent stimulus. Thus, to ensure that we evoked afferent inhibition under standard conditions we first compared MEP amplitude following a single afferent stimulus (on the index or middle finger) for each of the different ISIs (i.e., 15, 30, 45, 60, and 75 ms) with the TMS-only MEP amplitude. Two tailed t-tests revealed significant inhibition for some ISIs for both the single index (i.e., ISI of 15 ms: M±SE=0.96±.08mV; t(16)=-2.28, *p*=.04; ISI of 45 ms: M±SE=0.93±.08mV; t(16)=-2.81, *p*=.01) and single middle (i.e., ISI of 45 ms: M±SE=0.83±.09mV; t(16)=-4.08, *p*=.001; ISI of 60 ms: M±SE=-0.83±.09mV; t(16)=-4.72, *p*=.0001) finger stimulation conditions.

Next, we investigated whether MEP amplitudes on double afferent stimulation trials differed from those on single afferent stimulation trials by normalising MEP amplitudes on double trials to amplitudes on single index afferent stimulation trials (MEP ratio – Figure 2). A three-way repeated measures ANOVA (CONDITION x DELAY x TOUCH-TMS ISI) showed significant main effects of DELAY ($F(1,16)=6.19$, $p<.024$, $MSE=.19$, $\eta_p^2=.28$) and CONDITION ($F(1,16)=8.41$, $p<.01$, $MSE=.04$, $\eta_p^2=.34$), as well as an interaction between DELAY and CONDITION ($F(1,16)=4.75$, $p<.04$, $MSE=.1$, $\eta_p^2=.23$). The main effect of delay was due to the fact that motor cortex excitability was lower when the delay between the two tactile stimuli was 125 ms than when it was 30 ms ($t(16)=2.49$, $p=.024$). At the long delay, MEPs were equally inhibited at each ISI regardless of whether the stimulated fingers were the same (M±SE=84±7%) or different (M±SE=85±.5%; *p*=.8). At the short

delay, however, MEPs were larger (less inhibited) when the stimulated fingers were the same (M±SE=103±5%) than when they were different (M±SE=90±3%; *p*=.004).

Two tailed t-tests comparing MEP amplitude on double afferent stimulation trials with MEP amplitude on single index afferent stimulation trials showed that for the 30 ms delay (panel A) inhibition was significant for two middle-index conditions (i.e., 30 ms ISI: t(16)=-4.48, p=.0004; 75 ms ISI: t(16)=-2.97, p=.009) but not for any of the index-index conditions (All ps>.1), while for the 125 ms delay (panel B) there was significant inhibition for some ISIs for both middle-index (ISIs of 15 ms: t(16)=-5.09, p=.0001; 30 ms: t(16)=-2.36, p=.03; 45 ms: t(16)=-2.27, p=.04) and index-index (ISI of 30 ms: t(16)=-2.51, p=.02; 45 ms: t(16)=-3.22, p=.005; 75 ms: t(16)=-2.18, p=.04) conditions. Thus, under certain conditions CSE was significantly reduced when TMS was preceded by two tactile stimuli applied to either the same or different fingers than by a single stimulus applied to the index finger.

To verify that these results were not related to our normalisation procedure (double afferent stimulation trials normalised to single index afferent stimulation trials) we also analysed our data by normalising double afferent stimulation trials to TMS-only trials. The three-way repeated measures ANOVA revealed identical results, with main effects of DELAY (F(1,16)=5.30, p<.035, MSE=1342, η_p^2=.25) and CONDITION (F(1,16)=6.84, p<.019, MSE=234, η_p^2=.30), as well as an interaction between DELAY and CONDITION (F(1,16)=5.37, p<.034, MSE=324, η_p^2=.25). As in the previous analysis, at the long delay MEPs were equally inhibited at each ISI regardless of whether the stimulated fingers were the same (M±SE=75±5%) or different (M±SE=75±4%; *p*=.9). At the short delay, however, MEPs were larger (less inhibited) when the stimulated fingers were the same (M±SE=89±5%) than when they were different (M±SE=80±4%; *p*=.004).

Overall, these data show that when the two tactile stimuli were separated by 30 ms the subsequently evoked motor response was inhibited less by stimuli applied to the same finger

(index-index) than to two different fingers (middle-index). In contrast, when the two tactile stimuli were separated by 125 ms they inhibited a motor response by the same amount, regardless of whether they were delivered to the same or different fingers.

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Discussion

In the present study we used a double afferent inhibition paradigm with two different delays between the tactile stimuli to investigate the transfer of spatial information between the somatosensory and motor cortices. We found that two consecutive electrocutaneous stimuli inhibited TMS-induced motor responses in FDI, and that motor responses were smaller (more inhibited) when the tactile stimuli were separated by a long (125 ms) than a short (30 ms) delay. Importantly, same finger stimulation produced *less* inhibition than different finger stimulation *only* when the two stimuli were separated by a short delay. Since afferent inhibition is thought to arise from inhibitory connections from the somatosensory to motor cortices (Sailer *et al.*, 2003; Udupa *et al.*, 2009; Murray & Keller, 2011), and since the reduced response of the somatosensory cortex to repeated presentations of the same stimulus within short delays is well known (e.g., Chung *et al.*, 2002; Ragert *et al.*, 2008; Wühle *et al.*, 2011; Gatica Tossi *et al.*, 2013), we argue that the topological information present in the somatosensory cortices can be transferred to the motor cortex. The smaller somatosensory response after same versus different finger stimulation appears to result in weaker inhibitory inputs to the motor cortex and less inhibition of the TMS-evoked motor response. The existence of direct connections between the sensory areas in the post-central gyrus and the motor areas of the precentral gyrus has been demonstrated by Catani

and colleagues who, using diffusion tractography, revealed the presence of U-shape fibres that directly connect the primary somatosensory cortex with the motor cortex (Catani *et al.*, 2012). These fibres are thought to connect the somatosensory and motor areas of the cortical regions that are involved in the control of finely tuned movements and complex motor skills (i.e., the hand's brain regions).

Interestingly, while sensory-to-motor inhibition was similar for same versus different finger stimulation at the long delay (125 ms) the two afferent stimuli were not processed as fully independent events, as MEPs were smaller when the two stimuli were separated by 125 ms than by 30 ms. Thus, at least for the hand, information about both when and where tactile stimuli occur is processed within the somatosensory neural network and reflected in the output of the motor cortex when probed with single-pulse TMS.

In our short delay condition both the first and second cutaneous stimuli precede the TMS pulse by between 15 and 105 ms, delays that are generally considered to generate SAI (Delwaide & Olivier, 1990; Chen *et al.*, 1999; Sailer *et al.*, 2003; Voller *et al.*, 2006; Udupa *et al.*, 2009; although they have also been associated with facilitation; see Tamburin *et al.*, 2001; Kessler *et al.*, 2005). In contrast, for our long delay condition the second stimulus occurs within the SAI window, but the first stimulus (between 140 and 200 ms before the TMS pulse) occurs between those ISIs generally agreed-upon as evoking SAI and those thought to evoke long afferent inhibition (Chen *et al.*, 1999; Chen, 2004). Thus, the inhibition effects that we observe in both our short and long double stimulation conditions likely reflect the effects produced by each cutaneous stimulus, with a mixture of SAI and LAI effects being possibly present in the long delay condition.

Reduced corticospinal inhibition after same finger stimulation

The physiological repetition suppression response was originally described in single cell recordings (Gross *et al.*, 1972; Tanaka *et al.*, 1991). More recently, neural repetition suppression mechanisms have been inferred from decremented levels of cerebral blood flow using fMRI (Grill-Spector & Malach, 2001; Lingnau *et al.*, 2009), and are thought to underlie the behavioural results reported using TMS-adaptation paradigms (e.g., Cattaneo et al., 2011; Guzman-Lopez et al., 2011; Perini et al., 2012). We recently studied tactile adaptation of the fMRI BOLD response by delivering pairs of vibrotactile stimuli to the fingertips of the index and middle fingers of both hands (Tamè et al., 2012; see also Li Hegner *et al.*, 2007, 2010). We found that there was a greater reduction in the activation (i.e., BOLD response) in the primary and secondary somatosensory cortices after stimulation of the same (index-index) than different fingers (middle-index), suggesting that these areas clearly distinguish between the cortical representations of adjacent fingers. Moreover, we observed that tactile stimuli induced *deactivation* in the primary motor cortex (i.e., negative BOLD response), and that the deactivation pattern mirrored the activation pattern observed in the somatosensory cortices. That is, there was less motor deactivation when double touches were delivered to the same than different fingers (Tamè *et al.*, 2012). As no other tactually responsive area of the brain showed a pattern consistent with tactile adaptation, the primary motor cortex deactivation was attributed to modulations originating in the somatosensory cortices (Tamè *et al.*, 2012). The pattern of motor cortex modulation observed in the present experiment suggests that even though the somatosensory cortices modulate their activity as a function of the topology and timing of afferent events, the transfer of this information to the motor cortex is constrained by the temporal aspects of the afferent stimuli. At short delays, motor cortex excitability reflects information about the presence and location of afferent events, whereas at longer delays the

presence of multiple afferent events is communicated to the motor cortex, but location information is lost. Thus, this modification of the classical SAI paradigm, in which a single touch at the periphery precedes TMS over the motor cortex (Delwaide & Olivier, 1990; Tokimura *et al.*, 2000; Udupa *et al.*, 2009) provides an additional means by which to explore the topological features of sensorimotor connections as well as their temporal dynamics.

Spatial transfer of afferent inhibition

The interactions we observed within the short delay condition are consistent with the well-known temporal (Allison *et al.*, 1992; Mauguière *et al.*, 1997) and structural (Schweizer *et al.*, 2001; Nelson & Chen, 2008) response profile of SI after paired stimulation (e.g., Wühle *et al.*, 2011). The estimated persistence timing of a tactile stimulus in contralateral SI is at least 60 ms (Allison *et al.*, 1992; Mauguière *et al.*, 1997; Wühle *et al.*, 2011), well beyond the 30 ms interval between stimuli in our short delay condition. Thus, when separated by 30 ms (but not 125 ms) the processing of the two stimuli partially overlaps in time within SI. Given the well-defined somatotopic organisation of SI (Overduin & Servos, 2004; Martuzzi *et al.*, 2012), and fMRI data showing that it is sensitive to tactile repetition suppression (Tamè *et al.*, 2012), it is likely that alterations in SI activity are responsible for the finger-specific reduction in corticospinal excitability we observed at the short delay, although changes in spinal and/or subcortical circuits (e.g., direct thalamo-motor cortex projections) might have also contributed to the pattern of results we observed.

The absence of any difference in double afferent inhibition between same and different finger stimulation at the 125 ms delay suggests that when two stimuli enter somatosensory processing with a larger temporal separation topologic information is either lost or treated in such a way that it is no longer transferred to the motor cortex. Indeed, our 125 ms delay is longer than

the 110 ms estimated recovery time of a tactile signal in SI (Hamada *et al.*, 2002). While the precise definition of the temporal window within which spatial information is retained in SI and then transferred to the motor cortex was outside the scope of the study, we suggest that 125 ms between afferent stimuli is too long to preserve spatial information pertaining to the first stimulus. However, at this timing two subsequent stimuli still undergo some degree of integration, as they potentiate the inhibitory effect of the first stimulus. This interpretation is consistent with paired-pulse suppression studies of somatosensory cortex excitability which show that in SI the longer the delay between two afferent stimuli the smaller the reduction in the amplitude of the somatosensory evoked/field potential (McLaughlin & Kelly, 1993; Stevenson *et al.*, 2012), and that in SII this pattern is reversed (Wühle *et al.*, 2011).

The "time selective" sensory-motor interactions we demonstrate here are likely to be important for haptic control (Johansson & Flanagan, 2009), as complex hand-object interactions require closely timed events to be precisely localised in space, whereas the spatial resolution of more distant events is less critical.

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Figure caption

Figure 1. Schematic representation of the experimental conditions showing the four different double finger stimulation conditions and the timing between afferent stimuli and TMS pulses.

Figure 2. Normalised mean MEP amplitudes following double finger stimulation when the afferent stimuli were separated by a short delay (panel A) and a long delay (panel B). Open circles represent stimulation of the same finger twice (i.e., index-index) and solid circles represent stimulation of two different fingers (i.e., middle-index). Error bars indicate the Standard Error of the Mean (±SEM).