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ORIGINAL PAPER

Change-Driven M100 Component in the Bilateral Secondary Somatosensory Cortex: A Magnetoencephalographic Study

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Abstract

Our previous demonstration that the M100 somatosensory evoked magnetic field (SEF) has a similar temporal profile, dipole orientation and source location whether induced by activation (ON-M100) or deactivation (OFF-M100) of electrical stimulation suggests a common cortical system to detect sensory change. While we have not recorded such change-driven components earlier than M100 using electrical stimulation, clear M50 responses were reported using both ON and OFF mechanical stimulation (Onishi et al. in Clin Neurophysiol 121:588–593, 2010). To examine the significance of M50 and M100 in reflecting the detection of somatosensory changes, we recorded these waveforms in 12 healthy subjects (9 males and 3 females) by magnetoencephalography in response to mechanical stimulation from a piezoelectric actuator. Onset and offset (ON and OFF) stimuli were randomly presented with three preceding steady state (PSS) durations (0.5, 1.5 and 3 s) in one consecutive session. Results revealed that (i) onset and offset somatosensory events elicited clear M50 and M100 components; (ii) M50 and M100 components had distinct origins, with M50 localised to the contralateral primary somatosensory cortex (cS1) and M100 to the bilateral secondary somatosensory cortex (iS2, cS2); and (iii) the amplitude of M50 in cS1 was independent of the PSS durations, whereas that of M100 in S2 was dependent on the PSS durations for both ON and OFF events. These findings suggest that the M50 amplitude in cS1 reflects the number of activated mechanoreceptors during Onset and Offset, whereas the M100 amplitude in S2 reflects change detection based on sensory memory for Onset and Offset stimuli at least in part. We demonstrated that the M50 in cS1 and M100 in S2 plays different roles in the change detection system in somatosensory modality.

Keywords M50 · M100 · PSS · Change

Abbreviations

ISI	Interstimulus interval
MEG	Magnetoencephalography
PSS	Preceding steady state
SEFs	Somatosensory magnetic fields
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex

Introduction

One of the most important functions of sensory processing is the rapid detection of changes in the sensory environment to trigger automatic shifts in attentional focus and facilitate the execution of appropriate responses, such as escape. In humans, a dedicated cortical network is sensitive to changes of various sensory modalities (Downar et al. 2000; Tanaka et al. 2009).

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Our previous studies demonstrated that somatosensory (Yamashiro et al. 2009a) and auditory (Yamashiro et al. 2009b) 'ON' and 'OFF' events elicit similar change-driven magnetoencephalographic (MEG) components, peaking at approximately 100 ms post the event, termed M100 or N1m depending on the sensory modality. Our results comparing the abrupt event (on or off) response with the preceding steady state (PSS) before the change (silence preceding 'ON' or constant stimulation preceding 'OFF') suggest that the changes automatically activate a cortical change detection network using a memory trace of the preceding state (Yamashiro et al. 2008). If so, such traces are predicted to be stronger for longer PSSs. In fact, the amplitude of the N1m component depended on the PSS durations (0.5, 1.5, 3 and 6 s) not only for the onset of a pure tone but also for its offset and change in auditory frequency (Yamashiro et al. 2011). In addition, the amplitude of the somatosensory P100 or M100 component response to a stimulus depends on the interstimulus interval (ISI) (Forss et al. 1994a; Hamada et al. 2003; Hari et al. 1993; Tanaka et al. 2008; Wikstrom et al. 1996), as is the auditory N1m (Hari et al. 1982; Sams et al. 1993; Tanaka et al. 2008). Therefore, M100 may be analogous to N1m as the change-driven component for the somatosensory modality.

In our previous MEG study (Yamashiro et al. 2009a), we found that ON-M100 and OFF-M100 components exhibited comparable time courses of activation, locations and dipole orientations, suggesting that they originate from the same or a spatially and functionally overlapping group of cortical neurons. If a similar or identical group of neurons respond to the onset and offset of the electrical stimulation, ON-M100 and OFF-M100 would have similar activation patterns for the PSS durations (i.e. before the change). A recent study showed that auditory M50 was the change-driven component in the auditory cortex (Nakagawa et al. 2014). We have not recorded change-driven components earlier than the somatosensory M100 component using the offset of electrical train pulses, but Onishi et al. (2010) recorded clear OFF-M50 responses in the contralateral primary somatosensory cortex (cS1) using a tactile stimulator driven by a piezoelectric actuator. Moreover, Onishi et al. (2013) showed that the amplitudes of M50 and M100 in cS1 depended on the number of activated mechanoreceptors and the intensity of electrical stimulation. Therefore, we speculated that M50 and M100 have similar functions in change detection, and that this tactile stimulus paradigm can be used to evaluate both the M50 and M100 components.

The present study aimed to clarify whether the activation patterns of M50 and M100 are similar between ON and OFF responses under three different PSS conditions (0.5, 1.5 and 3 s), which would support the physiological significance of M50 and M100 in automatically detecting somatosensory changes.

Methods

Subjects

Experiments were performed on 12 right-handed volunteers (age 20–32 years) in accordance with the Declaration of Helsinki. Experimental protocols were approved in advance by the ethics committee of the Niigata University of Health and Welfare, Niigata, Japan. Written informed consent was obtained from all subjects.

Somatosensory Stimuli

An array of eight tiny plastic pins (4.8 × 2.4 mm; similar to Braille) driven by a piezoelectric actuator (KGS, Saitama, Japan; Fig. 1A) was used to obtain somatosensory evoked magnetic fields (SEFs). Each pin was 1.3 mm in diameter and protruded 0.7 mm at peak activation, with a distance of 2.4 mm between adjacent pins. The mechanical delay from the onset of the trigger signal to the time when the pins reached their highest position (full protrusion) was 0.64 ms. In the present study, mechanical stimulation was applied to the tip of the right index finger. We used three PSS durations presented in random order within the same test session: 0.5, 1.5 and 3.0 s. Seventy trials were presented for each PSS duration (total 210 trials). Subjects were instructed to relax the stimulated digit and ignore the stimuli throughout the experiment. The pin was continuously presented to the tip of the right index finger under the onset condition. In contrast, the pin was removed under the offset condition. That is, we set the pin-on stimulation to be a change from no stimulus as a "steady state" (pin-off stimulation) and pin-off stimulation to be another change from the pin stimulation as a "steady state" (pin-on stimulation). Thus, PSS is composed of these three types of random stimuli (Fig. 1B, C).

MEG Recording and Analysis

Experiments were conducted in a magnetically shielded room. SEFs were recorded with a helmet-shaped 306-channel MEG system (Vector-view, Elekta Neuromag, Helsinki, Finland) comprising 102 identical triple sensor elements. Each sensor element comprised two orthogonal planar gradiometers and one magnetometer coupled to a multi-superconducting quantum interference device, thus providing three independent measurements of the magnetic field. The MEG signals were band-pass filtered (0.03–330 Hz) and sampled at 1000 Hz.

We performed multi-dipole brain electrical source analyses (BESA, NeuroScan, Roanoke, VA, USA), separating multiple synchronous sources of activity in the brain under

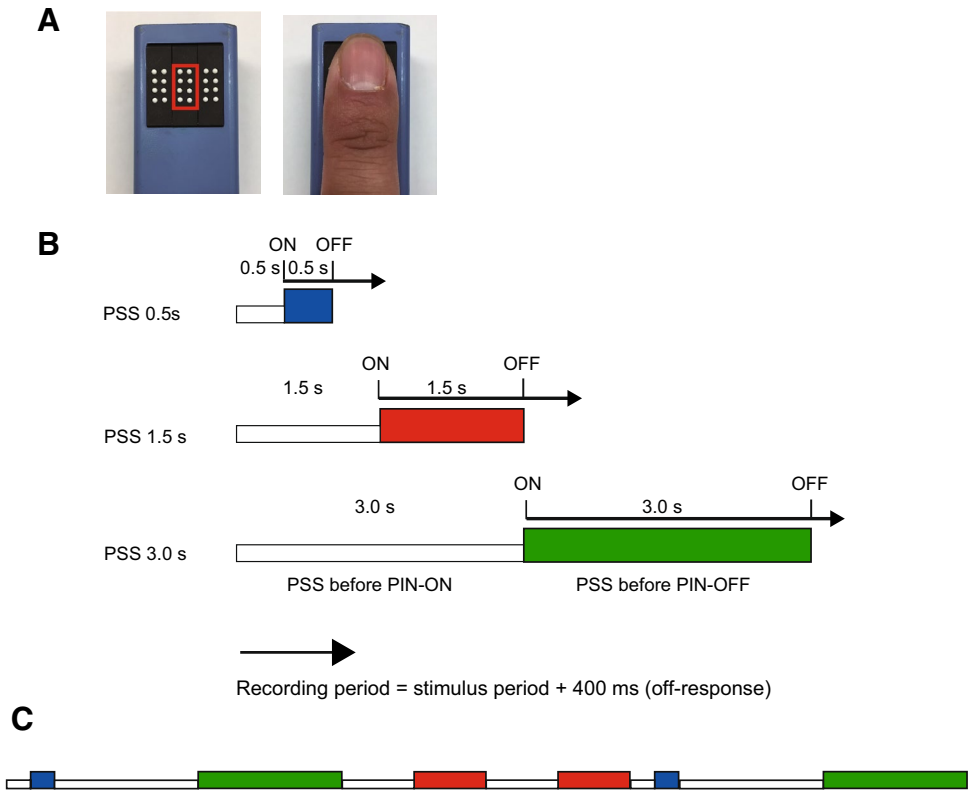

Fig. 1 Mechanical tactile stimulator, recording period and stimulation paradigm. **A** An array of eight tiny plastic pins (4.8 × 2.4 mm) driven by piezoelectric actuators. **B** Recording period included a pin-on period and an off-response period (400 ms) after pin-off. **C** The PSS duration of pin-on and pin-off periods was constant

the three conditions. The periods of analysis were 900, 1900 and 3400 ms depending on the PSS durations, including a 50-ms baseline period before the trigger. Trials with noise (> 3000 fT/cm) were automatically rejected from the analysis. Nonetheless, approximately 70 responses were averaged online for each condition in every subject. The averaged data were band-pass filtered at 1–50 Hz before analysis. The dipoles were estimated using only the ON response. The dipole model was assessed based on the following features: (1) percentage variance (Hari et al. 1988), (2) F ratio (the ratio of reduced chi-squared values before and after a new source was added) (Supek and Aine 1993) and (3) residual waveform (the difference between the recorded data and the model) (Inui et al. 2004). We continued to add a source to the model until the addition of a dipole did not significantly improve the fit relating robust M50 (40–60 ms) and M100 (80–140 ms) components. The peak GOF values of fit interval > 80% were considered to indicate a good model in each period. Finally, we compared only consistent three dipoles (cS1 and bilateral S2) in all subjects.

The four head position indicator (HPI) coils attached to the subject's head were measured with respect to three anatomical landmarks using a 3D digitiser, allowing alignment of the MEG and BESA system. The x-axis indicated the coronal plane with positive values toward the right preauricular point, the y-axis indicated the sagittal plane with positive values in the anterior direction and the z-axis indicated the transverse plane preauricular to the x–y plane with positive values toward the upper side. The location of each cortical source was converted to the Talairach–transformed standard brain in the BESA system. The peak amplitude of each source was subjected to a two-way repeated-measures ANOVA with a main factor event (Onset or Offset) and PSS duration (0.5, 1.5 and 3 s). The Greenhouse–Geisser epsilon was used to correct the degrees of freedom. Post hoc Bonferroni tests were performed to assess differences in the peak amplitude. Statistical significance was set at $p < 0.05$ for all tests.

Results

Localisation of M50 and M100 Components

Figure 2 shows superimposed waveforms from all channels and contour maps elicited by the ON and OFF events for all three PSS durations in a representative subject. We excluded two subjects from the analyses because dipoles could not be estimated reliably due to small responses under all three PSS conditions. The two events elicited clear M50 and M100 components in 10 of 12 subjects for all three PSS durations. The dipoles for M50 were localised to the cS1, and M100 dipoles were localised to the contra- and ipsilateral secondary somatosensory areas (cS2 and iS2). In all subjects, cS1

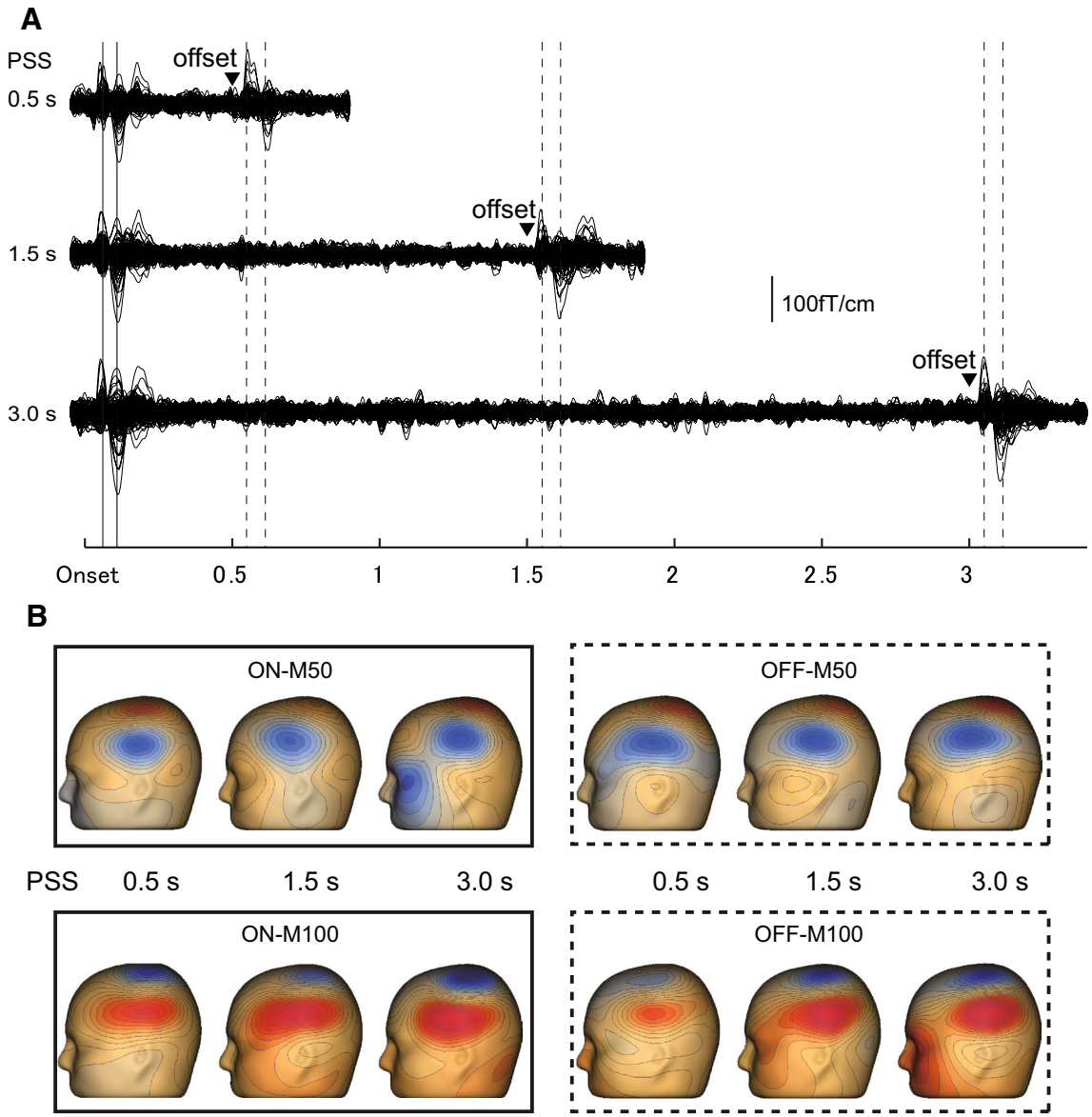

Fig. 2 Magnetoencephalographic responses to the onset and offset of pin stimulation to the right index finger. **A** Superimposed waveforms of all channels from a representative subject. On the time axis, pin-on stimulation occurs at 0 ms. The solid and dashed lines show the ON and OFF responses, respectively. **B** Iso-contour maps of M50 and M100 for the pin-on and pin-off periods under three PSS conditions. The M100 response in S2 has an unusual orientation resulting from temporally overlapping S1 and S2 activities

activities and bilateral S2 activities were distinct among PSS durations (Fig. 3; Table 1). However, we did not estimate dipoles for the Offset responses due to their small amplitudes. Using dipoles only from Onset trials may affect the outcome of statistical analysis.

Two-way ANOVA with event and PSS as main factors revealed the former as a significant factor influencing M50 amplitude in cS1 ($F_{(1, 9)} = 6.141$, $p < 0.05$, $\varepsilon = 1$), while PSS ($F_{(2,18)} = 1.061$, $p = 0.367$, $\varepsilon = 0.790$) and the event × PSS interaction ($F_{(2,18)} = 0.281$, $p = 0.758$, $\varepsilon = 0.869$) had no effect. Specifically, M50 amplitude in cS1 was greater for the ON event than the OFF event. In contrast, two-way ANOVA revealed the PSS duration as a significant factor influencing M100 amplitude in cS2 ($F_{(1.3,\ 11.701)} = 12.732$, $p < 18\ 0.01\ \varepsilon = 0.650$), while event had only a marginally significant influence ($F_{(1,9)} = 5.054$, $p = 0.051$, $\varepsilon = 1$) and the event × PSS interaction had no significant influence on M100 amplitude in cS2 ($F_{(1.269,\ 11.423)} = 1.659$, $p = 0.229$, $\varepsilon = 0.635$). Two-way ANOVA revealed that both the event ($F_{(1,\ 9)} = 8.736$, $p < 0.05$, $\varepsilon = 1$) and PSS duration ($F_{(1.629,\ 14.660)} = 16.383$, $p < 0.001$, $\varepsilon = 0.814$) were significant factors influencing the M100 amplitude in iS2, while the influence of the event × PSS interaction was not significant ($F_{(2,\ 18)} = 0.298$,

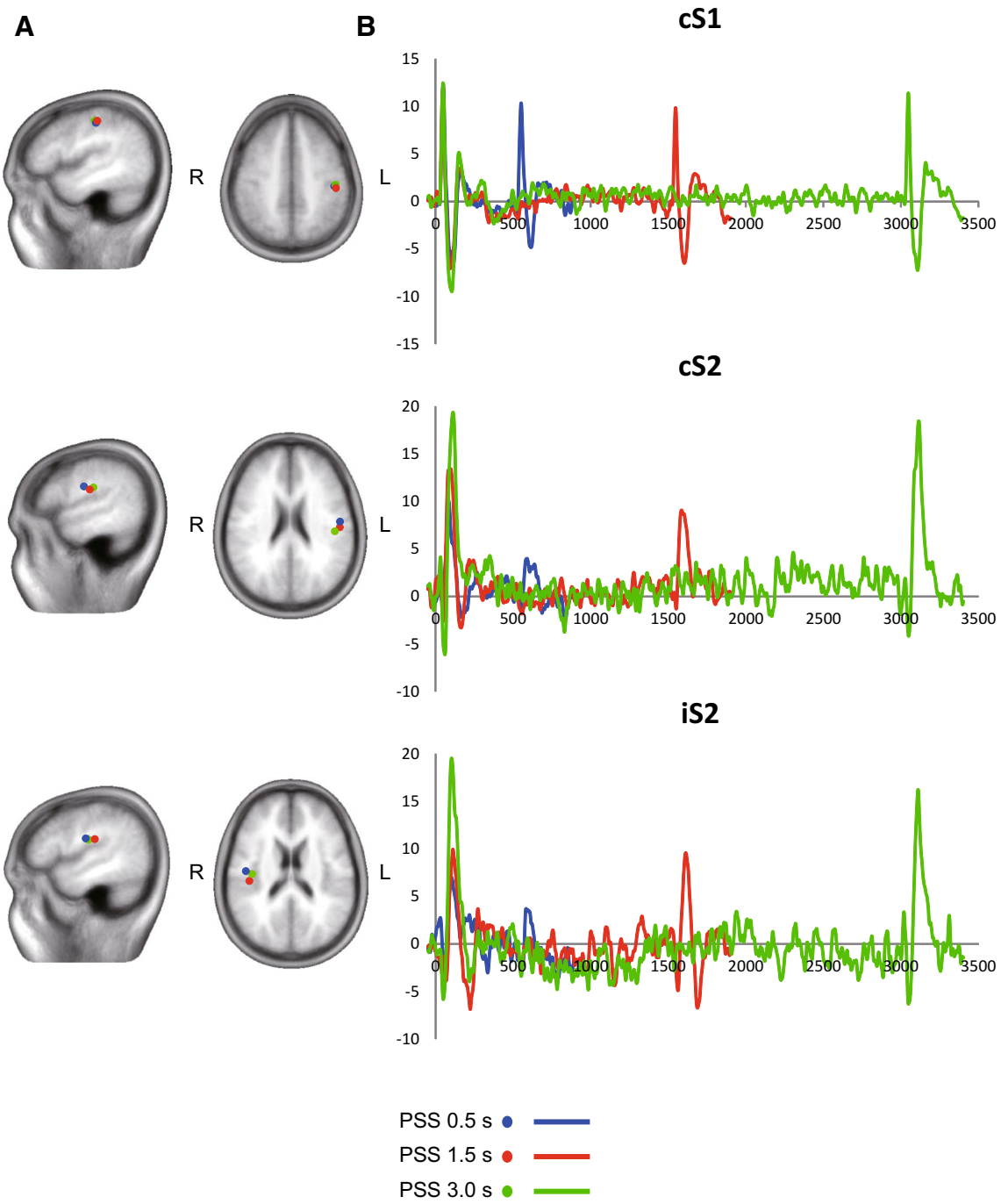

Fig. 3 Dipole mean location in standard brain and grand averaged waveforms **A** Mean locations of the primary and secondary somatosensory cortex and **B** grand averaged waveforms of cS1 and bilateral S2 activities under three PSS conditions

$p = 0.746$, $\varepsilon = 0.973$). Specifically, M100 amplitude in iS2 was greater for the ON event than the OFF event and increased with the PSS duration. Overall, M50 amplitude in cS1 and M100 amplitude in bilateral S2 were greater for ON than OFF events, and M100 amplitude in biralteral S2 were significantly greater at longer PSS durations (Figs. 4, 5).

Characteristics of M50 Amplitude in cS1 and M100 Amplitude in Bilateral S2 with Changing PSS Duration

The PSS duration had no effect on M50 amplitude in cS1 activity to either ON or OFF events (Fig. 4A), while M100

Table 1 Amplitude, latency and locations (mean ± SE) of the dipoles for the on- and off-responses under the three conditions

	Amplitude (nAm)		Latency (ms)		Location of dipoles (Tal)		
	ON	OFF	ON	OFF	x	y	z
cS1(M50)							
PSS 0.5 s	13.3 ± 1.1	10.8 ± 1.2	49.3 ± 1.3	50.1 ± 1.0	−44.4 ± 1.6	−23.5 ± 1.9	43.4 ± 2.2
PSS 1.5 s	12.2 ± 1.6	10.4 ± 1.1	46.0 ± 0.8	44.4 ± 1.0	−45.7 ± 1.5	−24.8 ± 3.6	45.4 ± 2.1
PSS 3.0 s	13.3 ± 1.3	11.6 ± 1.0	47.8 ± 1.0	42.8 ± 0.8	−45.1 ± 1.3	−22.2 ± 3.0	44.0 ± 1.8
cS2(M100)							
PSS 0.5 s	13.8 ± 3.3	7.6 ± 1.2	87.7 ± 5.0	111.2 ± 9.1	−51.1 ± 2.4	−11.4 ± 4.0	23.2 ± 9.6
PSS 1.5 s	18.3 ± 3.6	14.4 ± 1.9	97.4 ± 5.0	107.5 ± 11.9	−51.3 ± 2.3	−17.0 ± 3.5	20.3 ± 3.6
PSS 3.0 s	25.5 ± 4.1	25.2 ± 5.2	106.7 ± 7.5	105.4 ± 8.3	−45.8 ± 2.9	−21.4 ± 3.0	22.5 ± 2.7
iS2(M100)							
PSS 0.5 s	11.5 ± 1.8	6.7 ± 1.3	104.3 ± 5.3	98.2 ± 7.6	46.7 ± 3.4	−11.6 ± 4.1	21.3 ± 2.7
PSS 1.5 s	15.0 ± 1.6	12.3 ± 1.8	116.5 ± 5.0	116.7 ± 6.7	42.6 ± 2.1	−21.6 ± 3.7	20.1 ± 2.9
PSS 3.0 s	24.7 ± 3.5	20.2 ± 2.9	119.0 ± 8.3	120.1 ± 8.8	40.1 ± 2.8	−14.9 ± 3.0	19.3 ± 2.2

amplitude in bilateral S2 increased with the PSS duration for both ON and OFF events (Fig. 4B).

Discussion

In the present study, we investigated the somatosensory M50 and M100 components to clarify their physiological significance in the cortical memory-based sensory change detection network. Results showed that (i) the M50 and M100 waveforms were elicited by the onset and offset of mechanical stimulation, (ii) M50 and M100 components had distinct origins, with M50 localised to the contralateral primary somatosensory cortex (cS1) and M100 to the bilateral secondary somatosensory cortex (iS2, cS2); and (iii) the amplitude of M50 in cS1 was independent of the PSS duration, whereas that of M100 in bilateral S2 was dependent on the PSS duration for both ON and OFF events. Therefore, we suggest that the somatosensory M50 amplitude in cS1 is a stimulus-driven component related to the number of activated mechanoreceptors. On the other hand, the somatosensory M100 amplitude in bilateral S2 appears to be automatically elicited by any abrupt change, either stimulus ON or OFF, reflecting a change detected by comparing the new event (ON or OFF) with the PSS stored in short-term memory at least in part.

Stimulus-Driven M50 Component in cS1 Triggered by ON and OFF Stimulation

The somatosensory M50 component was elicited by both changes to the mechanical stimulus (ON and OFF). Onishi et al. (2010) reported that both ON-M50 and OFF-M50 components reflect inputs from rapidly adapting mechanoreceptors, such as Meissner's corpuscles and/or Pacinian corpuscles, which tend to fire only during the initial application of a mechanical stimulus or the removal of a constant mechanical stimulus. The dipole for ON-M50 was localised to the contralateral primary somatosensory cortex (cS1). Therefore, M50 amplitude in cS1 may faithfully reflect the number of activated mechanoreceptors. In fact, Onishi et al. (2013) found that both the number of pins and the inter-distance increased cS1 activity. In addition, Lin et al. (2003) used various levels of electrical pulse intensity at the wrist (1 − 6 × sensory threshold [ST]) and found that the lowest intensity (ST) stimulation evoked only M50, but not the N20m and P35m components of S1, and this M50 response increased as a function of stimulus intensity up to 3 × ST. Therefore, the M50 component of cS1 activity is conveyed by relatively low threshold afferent fibres. The cS1 activity recorded by these studies depended on the number of activated receptors, but not on the PSS duration. Therefore, the M50 component appears to be a stimulus-driven component, and S1 activity appears to reflect the degree of mechanoreceptor activation, but not sensory memory, to detect change.

Change-Driven M100 Component in Bilateral S2 Triggered by ON and OFF Events

A similar magnetic component peaking at approximately 80–140 ms was elicited by both ON and OFF events, which confirms previous findings (Yamashiro et al. 2009a). Therefore, it is possible that a similar group of neurons is responsible for this activity under both event conditions. The dipole for ON-M100 was localised to bilateral S2 (Fig. 3). Many studies have focused on the role of S2 using fMRI and MEG. In general, these studies have defined S2 as a secondary or higher-level processing area involved in attention (Burton et al. 1999; Kida et al. 2007; Mima et al. 1998), tactile texture discrimination (Ledberg et al. 1995), sensorimotor integration (Inoue et al. 2002;

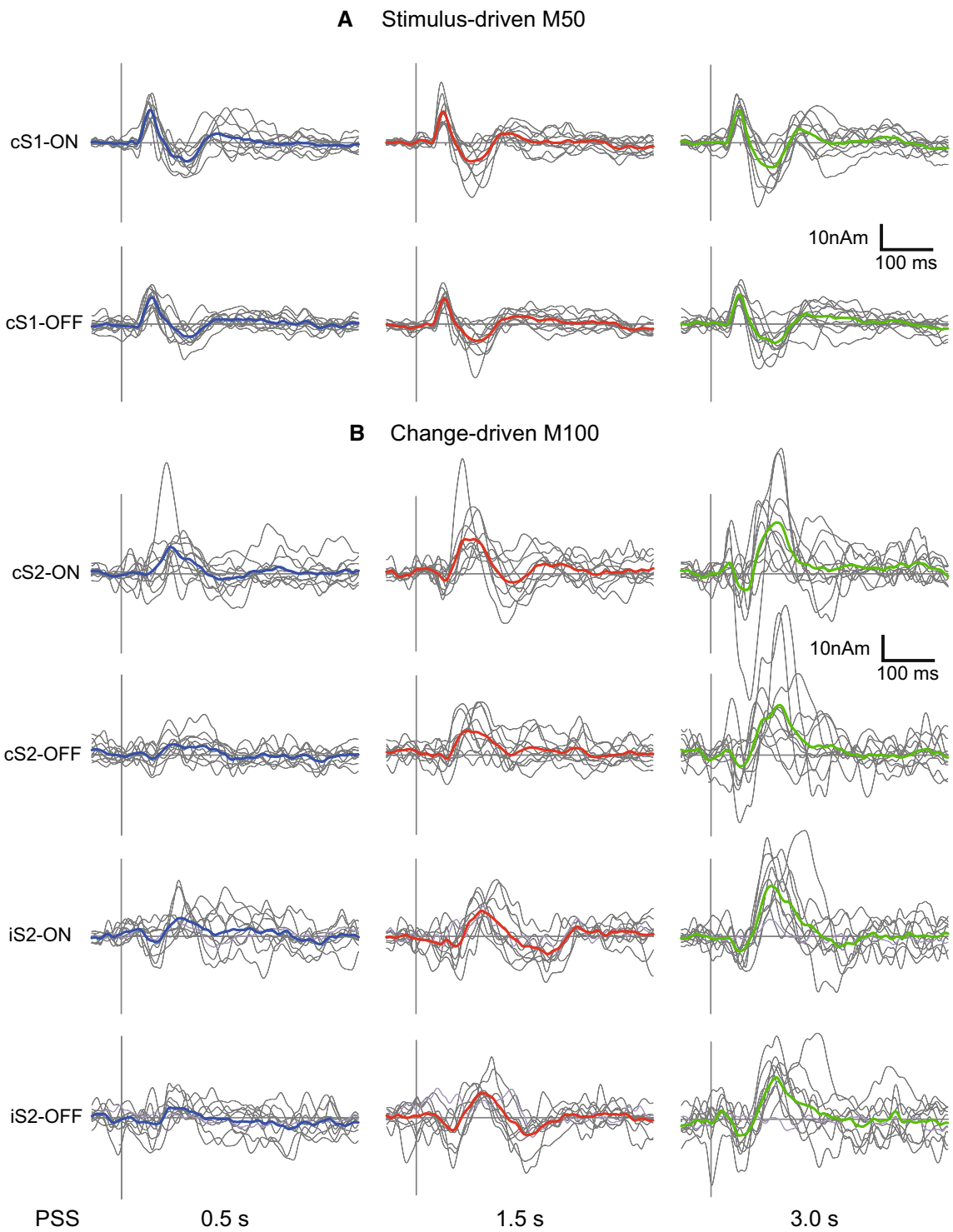

Fig. 4 Effects of the PPS duration on cS1 activity and bilateral S2 activities. Superimposed for all subjects (grey) and grand averages (solid colour) for pin-on and pin-off trials. **A** cS1. **B** Bilateral S2 activity

Kida et al. 2006a; Lin and Forss 2002; Wasaka et al. 2007) and integration of nociceptive and non-nociceptive inputs (Frot et al. 2001; Hari and Forss 1999; Inui et al. 2003a, b; Ploner et al. 1999). In addition, our previous finding that M100 in bilateral S2 was elicited by both the onset and offset of electrical stimuli suggests that it reflects the cortical response to the event change (on or off), irrespective of the nature of the change for the somatosensory

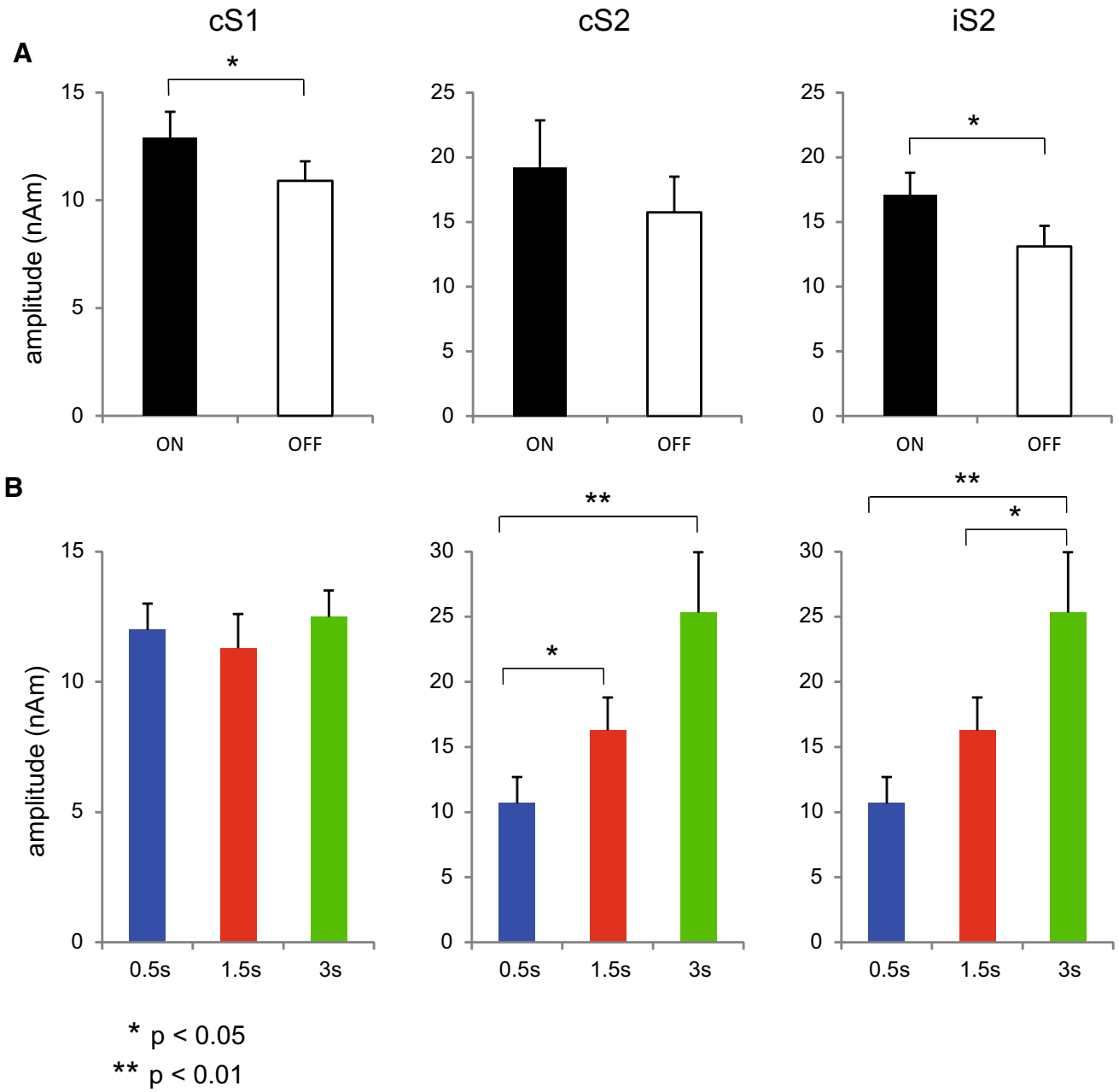

Fig. 5 The effect of event (**A**) and PSS duration (**B**) on cS1 and bilateral S2 activity

modality (Yamashiro et al. 2009a). These results are consistent with previous findings that S2 is involved in change detection (Downar et al. 2000; Tanaka et al. 2009). Therefore, detecting change may be one of the higher-level processing functions of the S2 region. This idea is consistent with the fact that the S2-M100 component is elicited by any kind of somatosensory stimulus, including electrical and mechanical stimulation (Disbrow et al. 2001; Forss and Jousmaki 1998; Simoes et al. 2002, 2001), air puffs (Forss et al. 1994b; Nguyen et al. 2005), vibration (Iguchi et al. 2007), and stimulus change (Yamashiro et al. 2009a; Otsuru et al. 2011; Naeije et al. 2018). These findings support the notion that the somatosensory M100 is related to the detection of any tactile event. That there is only one long-lasting M100 response regardless of stimulus duration also supports this idea. In our previous studies, one clear M100 component was elicited by a train of electrical pulses (Yamashiro et al. 2008). This suggests that the M100 component is not a stimulus-driven response, but rather a change-driven response.

The S1 and S2 Activities Reflect Different Functional Roles for Detecting Changes

Adaptation is a widely known phenomenon and includes processes such as a decrease in the cortical activity to repetitive stimulation among all sensory modalities (Grill-Spector et al. 2006; Näätänen and Picton 1987; Lampl and Katz 2017). In the somatosensory modality, adaptation is observed at all processing levels ranging from the afferent fibers (Bensmaia et al. 2005) to the cortical activity (Bradley et al. 2016; Chung et al. 2015). Bradley et al., (2016) have reported that adaptation in sensory cortices was seen as a mechanism allowing the creation of a transient memory mechanism. They recorded stronger adaptation profiles in S2 than in S1 and suggested that S2 plays a greater role in the sensory memory process. Several MEG studies also have shown that S1 and other higher-order somatosensory cortices have different adaptation profiles (Wikstrom et al. 1996; Venkatesan et al. 2014). That is, the S1 activity is almost constant for the ISIs whereas the S2 activity is variable for the ISIs.

As shown in Fig. 4, the bilateral S2 activity, and not the S1 activity, depended on the duration of the steady state preceding the change for both ON and OFF events. Therefore, the bilateral S2 activity cannot be explained only based the ongoing experience (change). Previous studies have demonstrated that the amplitude of ON-M100 depends on the ISI (Forss et al. 1994a; Hamada et al. 2003; Hari et al. 1993; Wikstrom et al. 1996). In addition, Raij et al. (2003) showed that S2 activity elicited by a laser increased as a function of the ISI peak at 160 ms. The dependence of bilateral S2 activity on the PSS for both ON and OFF events suggest that bilateral S2 activity reflects the inherent responsiveness to new sensory events. This notion is consistent with the proposal by Sokolov et al. (1963) that an orienting response is generated whenever a mismatch occurs between the established neuronal model and a new stimulus. In a previous EEG study, Kida et al. (2004, 2006) showed that ON-P100 is related to the orienting effect against a 'silent background'. Considering the present results and the previous findings, any kind of somatosensory stimulus change, including onset and offset, can activate the S2 neurons, and this activity could be affected by both adaptation as well as memory mechanisms. Future studies are warranted to clarify these mechanisms in detail.

Interestingly, our previous auditory study (Yamashiro et al. 2011) showed that the amplitude of auditory N1m linearly correlated with the log of the duration of the preceding state for all ON-N1m (sound onset following silence), OFF-N1m (silence following a sound) and change-related-N1m (change of tone frequency) responses. This implies that a common neural mechanism responds to a new event for each sensory modality.

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