

# Neural Basis of Early Somatosensory Change Detection: A Magnetoencephalography Study

G. Naeije<sup>1,3</sup> · T. Vaulet<sup>1</sup> · V. Wens<sup>1,2</sup> · B. Marty<sup>1</sup> · S. Goldman<sup>1,2</sup> · X. De Tiège<sup>1,2</sup>

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**Abstract** The mismatch negativity (MMN) reflects the early detection of changes in sensory stimuli at the cortical level. The mechanisms underlying its genesis remain debated. This magnetoencephalography study investigates the spatio-temporal dynamics and the neural mechanisms of the magnetic somatosensory MMN. Somatosensory evoked magnetic fields elicited by tactile stimulation of the right fingertip (*Single*), tactile stimulation of the right middle phalanx and fingertip (*Double*) or omissions (*Omitted*) of tactile stimuli were studied in different paradigms: in oddballs where *Double/Omitted* followed a sequence of four *Single*, in sequences of two stimuli where *Double* occurred after one *Single*, and in random presentation of *Double* only. The predictability of *Double* occurrence in oddballs was also manipulated. Cortical sources of evoked responses were identified using equivalent current dipole modeling. Evoked responses elicited by *Double* were significantly different from those elicited by *Single* at the contralateral secondary somatosensory (cSII) cortex. *Double* elicited higher cSII cortex responses than *Single* when preceded by a sequence of four *Single*, compared to when they were preceded by one *Single*. *Double* elicited higher cSII cortex response when presented alone compared to when *Double* were preceded

by one or a sequence of *Single*. *Omitted* elicited similar cSII cortex response than *Single*. *Double* in oddballs led to higher cSII cortex responses when less predictable. These data suggest that early tactile change detection involves mainly cSII cortex. The predictive coding framework probably accounts for the SII cortex response features observed in the different tactile paradigms.

**Keywords** Change detection · Mismatch negativity · Somatosensory · Adaptation · Magnetoencephalography · Predictive coding

## Introduction

Detecting changes or unexpected events in a sensory scene is vital to evolve safely and adapt to an ever-changing environment. To do so, the central nervous system has to efficiently isolate salient sensory inputs from irrelevant stimuli (for a review, see, e.g., Corbetta and Shulman 2011). Most of this filtering process remains unconscious and relies on the early detection of sensory changes within the environment (Downar et al. 2000).

The neural correlate of early sensory change detection has been largely studied for the auditory modality. A specific evoked response, coined the mismatch negativity (MMN), is typically observed in the electromagnetic brain signals for rare sounds (deviants) occurring amongst sequences of repeated sounds (standards) (for reviews, see, e.g., Näätänen et al. 2007; Garrido et al. 2009). The auditory MMN was initially discovered (Näätänen et al. 1978) and mainly studied with scalp electroencephalography (EEG) by subtracting evoked responses to standards from those elicited by deviants. The auditory MMN is characterized by a negative component peaking 100–250 ms post-deviant at midline

✉ G. Naeije  
gilles.naeije@erasme.ulb.ac.be

<sup>1</sup> Laboratoire de Cartographie fonctionnelle du Cerveau (LCFC), UNI – ULB Neuroscience Institute, Université libre de Bruxelles (ULB), Brussels, Belgium

<sup>2</sup> Department of Functional Neuroimaging, Service of Nuclear Medicine, CUB Hôpital Erasme, Université libre de Bruxelles (ULB), Brussels, Belgium

<sup>3</sup> Laboratoire de Cartographie fonctionnelle du Cerveau (LCFC), CUB Hôpital Erasme, 808, route de Lennik, 1070 Brussels, Belgium

central EEG electrodes (for a review, see, e.g., Näätänen et al. 2011). Its magnetic counterpart (mMMN) has also been described using magnetoencephalography (MEG) with a maximal response over bilateral temporal MEG sensors (Scherg and Berg 1991; Alho et al. 1993; Tiitinen et al. 1993; Wacongne et al. 2011).

In other sensory systems, mismatch responses to deviant visual stimuli are described around 135–150 ms post-deviant over occipital cortices (Cleary et al. 2013; Csibra and Czigler 1991; Czigler et al. 2007; Stefanics et al. 2014), while the somatosensory MMN (sMMN) typically peaks around 75–120 ms post-deviant with neural generators located at the contralateral primary (SI) or secondary (SII) somatosensory cortices (Akatsuka et al. 2005, 2007; Kekoni et al. 1997; Naeije et al. 2016).

Interestingly, despite the fact that the MMN has been discovered more than three decades ago, its neural mechanisms are still debated. Several non-mutually exclusive theories have been proposed to account for MMN genesis. In the *model adjustment* theory (Näätänen et al. 2007), the MMN is considered to reflect the neural detection of a deviation from a sensory memory trace based on preceding standard stimuli. By contrast, in the *adaptation* theory (May and Tiitinen 2010), the MMN is viewed as a mere subtraction artifact between the attenuated response of feature specific neurons to repeated standard stimuli and the response from sensory specific neurons sensitive to deviants. This adaptation theory shares similar features with the “rate effect” hypothesis proposed by some authors and in which the difference in amplitude observed between standards and deviants is thought to result from differences in stimulus repetition rates for standard and deviant stimuli (Hari et al. 1990). The rate effect hypothesis, which could be explained by an adaptation phenomenon, was initially supported by an experiment in which no difference was found between responses to deviants embedded among standards or presented alone with similar rate of occurrence (Hari et al. 1990). Still, that evidence was later contradicted in subsequent studies where responses to deviants and standards presented alone with similar rate of occurrence were found to be different from those presented in oddball paradigms (Forss et al. 1995; Kekoni et al. 1997). Finally, according to the *predictive coding* theory, the brain predicts incoming sensory information based on previous experience and discards expected information to allocate neural resources only to novel or surprising information (for a review, see, e.g., Friston 2010). This theory has gained increasing interests as it allows to combine the adaptation (Jääskeläinen et al. 2004; May and Tiitinen 2010) and the model adjustment (Garrido et al. 2009) theories for MMN genesis by considering (1) that the MMN is generated by specific neuronal error prediction units when a deviant incoming sound fails the prediction of higher level cortices for incoming sound (adjustment), and

(2) that activity of such error prediction units is modulated by the reproducibility of incoming stimuli (adaptation) (for a review, see Garrido et al. 2009). This theory might also explain why infrequent deviants embedded among standards or presented alone with identical rates of occurrence might share similar levels of surprise or expectation.

Empirical evidence supporting the predictive coding theory for the MMN neural mechanisms mainly comes from auditory (Wacongne et al. 2011; Chennu et al. 2013, 2016) and visual (Nirenberg et al. 2010) experiments. Surprisingly, experiments investigating the neural bases of the sMMN under this framework are scarce. By showing that the amplitude of the sMMN generated at SII cortex can be modulated by the predictability of deviant occurrence (i.e., smaller amplitude when more predictable), we provided novel data suggesting that the predictive coding theory might also account for the sMMN mechanism (Naeije et al. 2016).

In the present MEG study, we investigated further the neural mechanisms involved in early somatosensory change detection. To do so, we focused on the first 200 ms post stimulus onset, which is the timeframe previously reported as being involved in early change detection for the somatosensory modality (Shinozaki et al. 1998; Akatsuka et al. 2005; Restuccia et al. 2007; Butler et al. 2012; Strömmer et al. 2014; Naeije et al. 2016). For that purpose, we compared the cortical responses obtained in five different mechanical unilateral tactile paradigms adapted from previous auditory MMN studies (Hari et al. 1990; Kekoni et al. 1997; Jääskeläinen et al. 2004; Bekinschtein et al. 2009; Wacongne et al. 2011). The rationale guiding this study was that the comparison and the integration of the cortical responses obtained in those different tactile paradigms would bring novel insights into the neural mechanisms involved in sMMN genesis (i.e., model adjustment, adaptation/rate effect or predictive coding theories). In practice, we used two distinct tactile pneumatic stimuli: (i) tactile stimulations applied to the right index fingertip (*Single, S*), and (ii) tactile stimulations simultaneously applied to the middle phalange and the fingertip of the right index finger (*Double, D*). Omitted tactile stimuli (*Omitted, O*) were also used in one additional experimental conditions. In a first oddball paradigm adapted from Bekinschtein et al. (2009), *Single* and *Double* stimuli were gathered into blocks of five stimuli (i.e., SSSSD) that were repeated at a fixed and short interval to subsequently transiently and randomly deviate from the learned block pattern. This paradigm aimed at testing the effects of the modulation of *Double* stimulus occurrence predictability on magnetic sMMN (msMMN) responses. In a second paradigm adapted from Jääskeläinen et al. (2004), blocks composed of a *Single* stimulus directly followed by a *Double* stimulus were used to determine whether *Double* stimuli elicited similar cortical responses in such situation as in the previous oddball paradigm (Jääskeläinen et al. 2004) or if the response amplitude

was attenuated. In a third paradigm adapted from Kekoni et al. (1997), only *Double* stimuli were randomly presented to assess the difference in cortical responses with those elicited by such stimulus in the two previous paradigms. The fourth paradigm was similar to the first oddball paradigm except that the inter-block interval (IBI) became longer and randomly set. Modulation of the IBI was used to assess the existence of cortical response attenuation between the first and the last *Single* stimulus in each block and the potential impact of such attenuation phenomenon on msMMN amplitude. Finally, in a paradigm adapted from the first oddball paradigm and from Wacongne et al. (2011), *Double* stimuli were simply replaced by *Omitted* stimuli. This paradigm was used to test the existence of cortical responses locked to the absence of a predictable tactile stimulation.

By exploring the cortical responses elicited by the different experimental paradigms used in this study, we aimed at establishing the role of the different theories (i.e., model adjustment, adaptation/rate effect, predictive coding) elaborated for the auditory modality in the neural mechanisms involved in early somatosensory change detection.

## Materials and Methods

### Subjects

Sixteen healthy adult subjects (mean age: 29 years  $\pm$  3 SD, 7 females) who participated in a previous study (Naeije et al. 2016), contributed to the present study (Group A). Additionally, seven of these subjects and three novel right-handed healthy adults subjects participated in complementary experiments (Group B, ten subjects, mean age: 30 years  $\pm$  4 SD, 7 females).

All subjects were right-handed according to the Edinburgh handedness inventory (Oldfie 1971). They participated in the study after written informed consent. The study was approved by the ULB-Hôpital Erasme Ethics Committee (Reference EudraCT/CCB: B406201317212).

### Experimental Paradigm (Fig. 1)

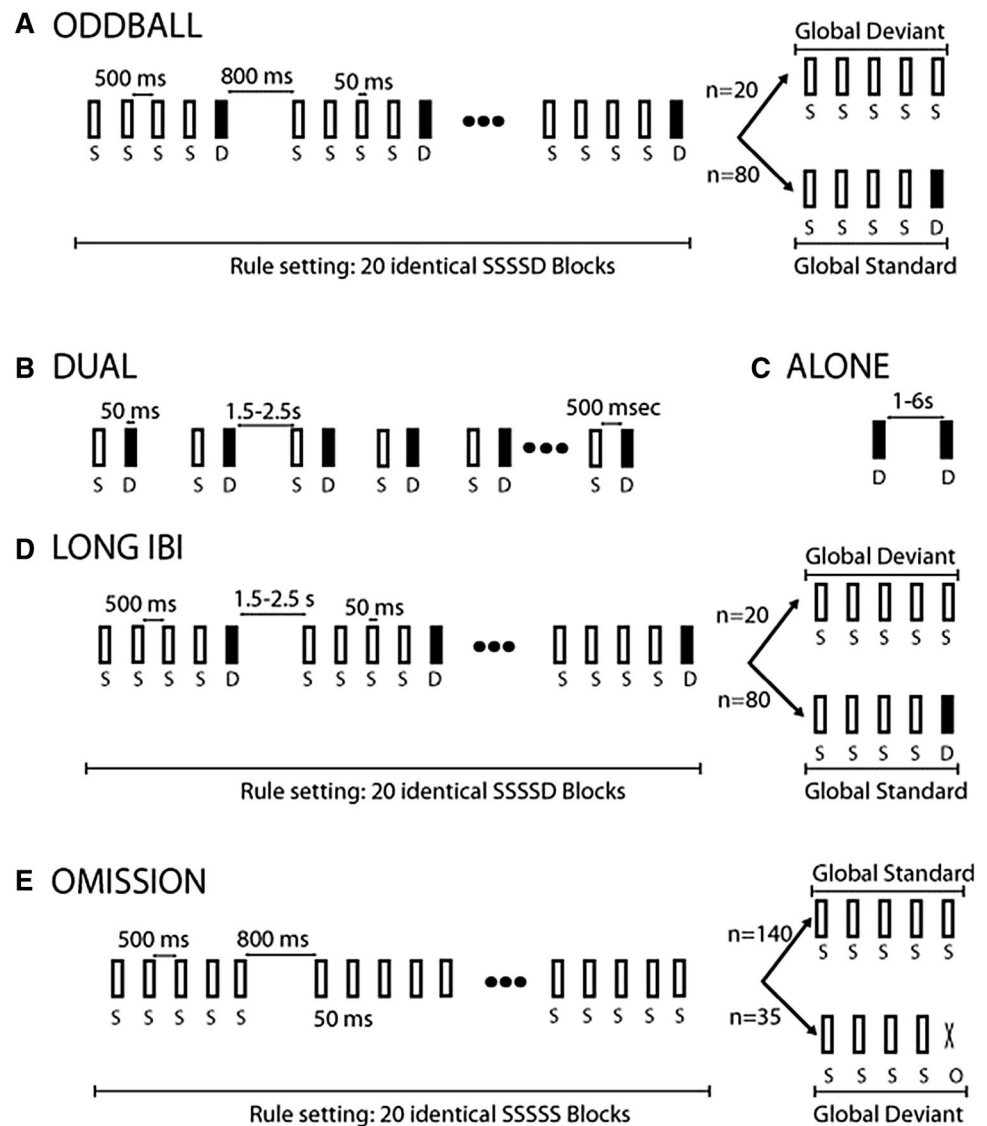
During MEG recordings, subjects sat with their forearms lying on the MEG table, palms down. They were instructed to gaze at a cross on the wall of the magnetically shielded room (MSR). Pneumatic tactile stimuli were chosen over peripheral nerve electrical stimulation because they are more natural and pleasant than electrical stimuli, and because electrical stimuli activate simultaneously a large number of fibers with different conduction velocities and bypass peripheral mechanoreceptors as well as the distal part of the peripheral nerves.

Tactile stimulations (duration: 50 ms) were performed with a homemade pneumatic stimulator that used circular synthetic membranes as in Wienbruch et al. (2006). The membrane covered an area of 1 cm<sup>2</sup> and pneumatic stimulation used an intensity of two bars for all stimuli (one membrane for *Single* stimuli and two membranes for *Double* stimuli). Earplugs were used to suppress the auditory noise associated with the pneumatic stimulation. In the present study, we chose to apply the *Single* and *Double* stimuli in oddball paradigms on the same finger to recruit as much as possible common peripheral and cortical pathways between different tactile stimuli.

All subjects belonging to Group A underwent three experimental conditions (“Oddball”, “Dual”, and “Alone”) that were applied in random order. Of notice, the experimental paradigm and the results of the *Oddball* condition have already been reported in details in Naeije et al. (2016).

In the *Oddball* condition (Fig. 1a), subjects underwent a unilateral tactile oddball paradigm adapted from the auditory “local/global” oddball paradigm of Bekinschtein et al. (2009). In this condition, standards corresponded to *Single* tactile stimulations (i.e., one synthetic membrane applied to the right index fingertip), while deviants consisted in *Double* tactile stimulations (i.e., one synthetic membrane applied to the middle phalange and another to the fingertip of the right index finger). Blocks of five stimuli were applied with an inter-stimulus interval (ISI) of 500 ms, and either comprised four *Single* stimuli followed by a *Double* stimulus (local deviation, SSSSD blocks) or five *Single* stimuli (SSSSS blocks). One hundred and twenty blocks (IBI: 800 ms) were administered to each subject. The first 20 blocks were always SSSSD blocks (standard blocks with local deviance), so that subjects could identify standard blocks as the rule. In the subsequent 100 blocks, 20 SSSSS blocks (deviant blocks with global deviance but no local deviance) were pseudorandomly intermingled among SSSSD blocks (two deviant blocks could not occur successively and had to be separated by at least one standard block). Subjects were asked to count the number of deviant blocks. In Naeije et al., this condition allowed us to monitor the effects of the modulation of deviant occurrence predictability on the msMMN by studying how the introduction of deviant blocks (SSSSS blocks) modulated the cortical responses to local deviants (i.e., *Double* stimuli); local deviants generating an early change detection response. To do so, we compared the msMMN responses elicited by *Double* stimuli (local deviants, in SSSSD blocks) occurring before and after each deviant block (SSSSS blocks). The results described in Naeije et al. (2016) using this *Oddball* condition will be briefly summed up in the “Results” section of the present paper. Of notice, this condition was also used here to search for a significant difference in somatosensory evoked fields (SEFs) elicited by the first and the fourth *Single* stimuli of each SSSSD block.

**Fig. 1** Somatosensory paradigms used in this study. **a Oddball** condition: Blocks of five stimuli either comprised four *Single* stimuli followed by a *Double* stimulus (SSSSD blocks) or five *Single* stimuli (SSSSS blocks). Each *Double* stimulus in SSSSD blocks (local deviation), by breaking a sequence of four identical stimuli, elicited a msMMN response. **b Dual** condition: Blocks of two stimuli comprising a *Single* stimulus followed by a *Double* stimulus. **c Alone**: *Double* stimuli separated by long and random interstimulus intervals. **d Long\_IBI\_Oddball**: same as in *Oddball* except that longer and random interblock intervals were used. **e Omission** condition: Blocks of five stimuli either comprised five *Single* stimuli (SSSSS blocks) or four *Single* stimuli followed by an Omitted stimulus (SSSSO blocks). SSSSS blocks were used as standard blocks with no local deviation, while SSSSO blocks were used as global deviants with local deviation



In the *Dual* condition (Fig. 1b) adapted from Jääskeläinen et al. (2004), 80 blocks composed of a *Single* stimulus directly followed by a *Double* stimulus, were applied with a constant ISI of 500 ms and a random IBI ranging from 1 to 6 s. This condition was used to assess if *Double* stimuli elicited similar cortical tactile change detection response (also henceforth referred to as msMMN for easiness) after one *Single* stimulus than those recorded after a sequence of *Single* stimuli as in the *Oddball* condition.

In the *Alone* condition (Fig. 1c), only *Double* tactile stimuli were delivered to subjects with a random ISI ranging from 1 to 6 s. This condition is adapted from previous MEG studies supporting the rate effect hypothesis, which have failed to find any difference between responses to deviants embedded in sequences of standards or presented alone with similar rate of occurrence. Here, we used a longer ISI for *Double* stimuli occurrence in the *Alone* and the *Dual*

conditions compared with the *Oddball* condition. This was done to test the hypothesis that such long ISI would increase the “surprise” associated with the occurrence of *Double* stimuli, and therefore lead to cortical responses of higher magnitude in the *Alone* than in the *Oddball* or the *Dual* conditions.

The ten subjects belonging to Group B underwent two additional and complementary experimental conditions (“*Long\_IBI\_Oddball*”, “*Omission*”) in a separate MEG session.

In the *Long\_IBI\_Oddball* condition (Fig. 1d), the experimental paradigm was similar to the *Oddball* condition except that the IBI was randomly set between 1.5 and 2.5 s. This condition was used to assess the existence of cortical responses attenuation between the first and the last *Single* stimuli in each standard block (i.e., SSSSD blocks) and the potential impact of such attenuation phenomenon on

msMMN amplitude. The rationale for this condition was that previous MEG studies disclosed significant decrease in the amplitude of cortical responses to electrical median nerve stimulations with decreasing ISI (and particularly at SII cortex), and mainly for ISI < 1 s (Mauguiere et al. 1997). Therefore, based on this finding, we hypothesized that increasing the IBI (>1 s) would increase the cortical response to the first *Single* stimulus of each SSSSD block compared with the subsequent *Single* stimuli, which would facilitate the investigation of an eventual brain responses attenuation as well as its consequences on msMMN responses.

Finally, subjects of Group B underwent an “Omission” condition adapted from Wacongne et al. (2011). In this oddball condition, deviants consisted in *Omitted* stimuli (i.e., the omission of tactile stimuli), while standards consisted in *Single* tactile stimuli (Fig. 1e). In this condition, 180 SSSSS blocks (standard blocks) were intermingled with 35 SSSSO blocks (deviant blocks). Deviant blocks were pseudorandomly inserted (two deviant blocks could not occur successively and had to be separated by at least one standard block). For this condition, ISI and IBI were similar to those used in the *Oddball* condition, and the first 20 blocks were always standard (i.e., SSSSS) blocks. This oddball paradigm was used to assess if omissions would lead to any cortical evoked response (Wacongne et al. 2011).

## Data Acquisition

Cortical neuromagnetic signals were recorded using a whole-scalp-covering MEG device (Vectorview, Elekta Oy, Helsinki, Finland) installed in a light-weight MSR (Maxshield, Elekta Oy, Helsinki, Finland), the characteristics of which have been described elsewhere (De Tiège et al. 2008). Of notice, the MEG sensor layout consisted in 102 sets, each comprising one magnetometer and two orthogonal planar gradiometers with different spatial sensitivity (i.e., lead field) to right beneath or nearby neural sources. Four head-tracking coils monitored subjects’ head position inside the MEG helmet. The locations of the coils and at least 150 head-surface (on scalp, nose and face) points with respect to anatomical fiducials were determined with an electromagnetic tracker (Fastrak, Polhemus, Colchester, VT, USA). Eye movements and blinks were monitored with vertical and horizontal electrooculograms (EOGs). Electrocardiogram (ECG) was monitored using bipolar electrodes placed below the clavicles. All signals were bandpass filtered at 0.1–330 Hz and sampled at 1 kHz.

Subjects’ high-resolution 3D-T1 cerebral magnetic resonance images (MRIs) were acquired on a 1.5 T MRI scanner (Intera, Philips, The Netherlands).

## Data Preprocessing and Sensor-Space Analyses

The preprocessing and the analyses pipelines used in this study are derived from Naeije et al. (2016) and will therefore be briefly described here.

Continuous MEG data were first preprocessed off-line with the signal space separation (SSS) method to subtract external interferences and correct for head movements (Taulu et al. 2005). Then, ocular and cardiac artifacts were eliminated from filtered data (off-line band-pass filter: 0.1–45 Hz) using independent component analysis as implemented in the FastICA algorithm (dimension reduction to 30, nonlinearity  $\tanh$ ) (Vigário 1997). To do so, artifactual components were identified using temporal correlations with EOG and ECG (correlation thresholds: 0.15) and visual inspection of their spatial topography (number of rejected components ranged from 2 to 5 across subjects). Time series of corresponding artefactual components were then regressed out from the raw data.

The open source Fieldtrip software (<http://fieldtrip.fcdonders.nl/>) was then used for further preprocessing. A common preprocessing pipeline that included MEG data epoching (epoch length: 800, –200 to +600 ms post-stimulation onset), thresholds for epoch rejection: 0.7 pT/cm for planar gradiometers and 3 pT for magnetometers, low-pass filtering at 45 Hz for all conditions except omission conditions where the low-pass was set at 20 Hz based on previous studies (Jääskeläinen et al. 2004; Restuccia et al. 2007; San-Miguel et al. 2013; Chennu et al. 2016), baseline correction (–150 ms to stimulus onset) and epoch averaging was used to uncover the SEFs of interest.

For the *Oddball*, *Long\_IBI\_Oddball* and *Omission* conditions, epochs corresponding to *Single* (intra-block averaging of the four standards), *Double* and *Omitted* stimuli were separately averaged. Furthermore, for the *Oddball* and the *Long\_IBI\_Oddball* conditions, additional averages of *Single* stimuli were computed, one for the first and another for the fourth *Single* stimulus within each SSSSD block. For the *Dual* condition, *Single* and *Double* stimuli were separately averaged. For the *Alone* condition, *Double* stimuli were averaged together. Individual-level averaged epochs obtained for each stimulus type and condition were also averaged across subjects (grand average).

Differences in the SEFs elicited by (1) *Single* and *Double/Omitted* stimuli in *Oddball*, *Dual*, *Long\_IBI\_Oddball* and *Omission*, (2) *Double* stimuli in *Oddball* and *Dual*, (3) *Double* stimuli in *Oddball* and *Alone*, (4) *Double* stimuli in *Dual* and *Alone*, (5) the first and the fourth *Single* stimulus of standard (i.e., SSSSD) blocks in *Oddball* and *Long\_IBI\_Oddball*, and (6) the first or the fourth *Single* stimulus and *Double* stimuli in *Long\_IBI\_oddball*, were then statistically investigated in the sensor space (signals from orthogonal planar gradiometers combined via their Euclidian norm)

between 20 and 220 ms post-stimulus onset at the subject level using the non-parametric clustering approach described by Maris and Oostenveld (2007). This clustering approach was used as it allowed identifying, without any a priori hypothesis, where and when significant sensor-space differences occurred between the evoked responses of interest. The time-window of investigation (20–220 ms) corresponded to the timeframe typically reported for early change detection and sMMN studies in EEG and MEG (Shinozaki et al. 1998; Akatsuka et al. 2005; Restuccia et al. 2007; Butler et al. 2012; Strömmer et al. 2014; Naeije et al. 2016). Briefly, t values assessing the response differences at each sensor and time sample were computed as well as their uncorrected p values (two-sided t-test; degrees of freedom: subject-level statistics = 598 for oddball/Omission paradigms, 158 for the *Dual paradigm* and 78 for the *Alone paradigm*, Group-level statistics = 14 for Group A and 8 for Group B). To address the multiple spatiotemporal comparisons (102 gradiometers' norms and 180 time samples), clusters of adjacent spatiotemporal points were obtained using a 0.05 threshold on those p values (with the constraint that at least two neighboring sensors are involved). Each cluster was weighted by their summed t values and the maximum weight over all clusters was taken as statistic. Its significance was then assessed non-parametrically with the Monte-Carlo approach, i.e., its p value was derived from a null distribution estimated using the maximum cluster weights of 1000 simulated datasets obtained by random permutations of stimuli/conditions labels in the different comparisons (see above) that were performed. This method has the advantage of not implying any spatiotemporal a priori hypothesis and allows localizing, using the maximum cluster at  $p < 0.025$  (two-sided test), where and when SEFs were significantly different (Naeije et al. 2016), notwithstanding interpretation issues discussed in Maris and Oostenveld (2007).

For group-level statistics, the differences investigated at the individual level were computed for each condition using a non-parametric cluster-based approach similar to that described above with the only difference that stimuli/conditions were randomly permuted subject-wise rather than epoch-wise (Naeije et al. 2016). Also, to search for an effect of the modulation of *Double* stimulus occurrence predictability on msMMN amplitude, we assessed using similar group-level non-parametric cluster-based approach the difference between *Double* stimuli within the standard SSSSD blocks occurring before and after deviant SSSSD blocks of the *Oddball* condition.

Then, the cortical generators of significant msMMN responses or differences between the responses elicited by *Single/Double* stimuli in different conditions (see above) were subsequently identified at the timeframe and the location of statistically significant sensor-level differences without any prior assumption about the location and the number

of cortical areas involved. To do so, conventional equivalent current dipole (ECD) modeling tools (Elekta Oy, Helsinki, Finland) and spherical conductor models determined from the subjects' MRI were used and based on an approach adapted from Salmelin (2010) and detailed in Naeije et al. (2016). In practice, to identify the cortical generators of the smMMN, magnetic field patterns were visually inspected in each subject during the period of statistically significant sensor-level differences and over the sensors determined by the non-parametric clustering approach. Clear dipolar field patterns were used in a nonlinear search to localize the corresponding source using, when appropriate, a selection of at least 40 sensors (planar gradiometers and magnetometers) centered over the maximal magnetic fields difference to optimize ECD spatial accuracy and avoid any influence of irrelevant magnetic signals. Only dipoles with a goodness of fit above 85% were considered relevant. When multiple sources were required to explain the magnetic field patterns, the number of ECDs was determined based on classical multipole modeling approaches that relied on: (1) the number of clear dipolar magnetic field patterns; (2) the correspondence between the original data and the predicted source activity at the sensor level of each source or their combination; (3) the use of source activity linear projection from original sensor level data; and (4) the goodness of fit (>85% for the time window of interest) of the multidipole modeling (Salmelin 2010). Finally, the source strength waveforms of each ECD over the whole epoch were obtained from the single or multipole model. Corresponding ECDs were then superimposed on the co-registered subjects' MRI.

Results of all statistical comparisons were considered significant at  $p < 0.05$ .

## Results

### Oddball Conditions

#### *Oddball* (Fig. 5)

We here sum up the results of the *Oddball* condition already described in Naeije et al. (2016). At the group level (Group A) and compared with *Single* stimuli, *Double* stimuli elicited a significant msMMN peaking at 70–100 ms post-deviant onset over the left central sensors with only one cortical generator compatible with SII cortex contralateral (cSII) to the stimulation (MNI coordinate, [x: -47, y: -22, z: 35] mm). At the individual level, a similar msMMN response was observed in 12 out of 16 subjects. Amplitude of the response at the cSII cortex was higher for *Double* than for *Single* stimuli (28 nAm  $\pm$  13.5 SD vs. 9.5 nAm  $\pm$  7.3 SD). At group level, the comparison between the SEFs elicited by *Double* stimuli within SSSSD blocks occurring before and after

SSSSS blocks disclosed a significant difference with a mean timeframe of 100–120 ms over left fronto-central sensors. The cortical generator of the difference was accurately modeled by a single ECD located at cSII cortex ( $[x: -47, y: -22, z: 35]$ ) with higher amplitude for *Double* stimuli occurring after a deviant SSSSS block than for those occurring just before ( $32.6 \text{ nAm} \pm 11.5 \text{ SD}$  vs.  $25.5 \text{ nAm} \pm 9.1 \text{ SD}$ ), resulting in higher msMMN amplitude ( $17.3 \text{ nAm} \pm 13.7 \text{ SD}$  vs.  $6.8 \text{ nAm} \pm 8.9 \text{ SD}$ ).

Finally, at the group-level, there was no difference between the first and the fourth *Single* stimuli within standard SSSSD blocks.

### Long\_IBI\_Oddball (Figs. 2, 5)

At the group level (Group B), the comparison between the SEFs elicited by the first and the fourth *Single* stimulus of SSSSD blocks disclosed a significant difference between 55 and 135 ms post-*Single* stimulus onset over the left fronto-central sensors. Eight out of ten subjects displayed similar significant difference over the left fronto-central sensors.

The cortical source at the origin of this sensor-space difference was accurately modeled by a single ECD located at cSII cortex contralateral to the stimulation ( $[-43, -19, 21]$ ). The difference was due to a substantial attenuation of cSII cortex responses amplitude between the first and the fourth *Single* stimuli ( $36.6 \text{ nAm} \pm 22.0 \text{ SD}$  vs.  $12.5 \text{ nAm} \pm 9.6 \text{ SD}$ ). Consequently, at group-level, the msMMN at cSII cortex ( $[-43, -19, 21]$ ) was significant only when computed using the fourth rather than an average of the four *Single* Stimuli of standard SSSSD blocks.

### Dual Condition (Figs. 3, 5)

A significant difference between the SEFs elicited by *Single* and *Double* stimuli was observed at the group level (Group A) from 55 to 145 ms post-deviant onset over the left fronto-central sensors. This effect was observed in 12 out of the 16 subjects.

As in the *Oddball* condition, the cortical generator of this difference was accurately modeled by a single ECD located at the left cSII cortex ( $[-43, -27, 28]$ ). But, unlike in the *Oddball* condition, the amplitude of cSII cortex sources was higher for SEFs elicited by *Single* compared with *Double* stimuli (cSII cortex:  $27.2 \text{ nAm} \pm 12.5 \text{ SD}$  vs.  $14.9 \text{ nAm} \pm 9.7 \text{ SD}$ ), leading to “mismatch” responses of opposite polarity in *Dual* versus *Oddball* conditions.

### SEFs Elicited by Double Stimuli in Oddball, Dual and Alone Conditions (Figs. 4, 5)

In Group A, a significant difference between the SEFs elicited by *Double* stimuli in *Oddball* and in *Dual* was observed

from 60 to 160 ms post-stimulus onset over the left fronto-central sensors. At the subject level, a similar statistically significant difference was observed in 15 out of the 16 subjects.

The cortical generators of this differences was accurately modeled by a single ECD at the left cSII cortex ( $[-43, -27, 28]$ ) with a higher source amplitude for SEFs evoked by *Double* stimuli in *Oddball* than in *Dual* at the left cSII cortex ( $20.5 \text{ nAm} \pm 14.7 \text{ SD}$  vs.  $13.5 \text{ nAm} \pm 11.2 \text{ SD}$ ).

A significant difference between the SEFs elicited by *Double* stimuli in *Oddball* and *Alone* conditions was also observed at the group level within the 50–165 ms post-stimulus onset over the left fronto-central sensors; an effect that was observed in all subjects.

The cortical generator of this difference was accurately modeled by a single ECD located at cSII cortex ( $[-42, -27, 25]$  mm) with higher cSII cortex amplitude in *Alone* than in *Oddball* ( $31.9 \text{ nAm} \pm 20.8 \text{ SD}$  vs.  $25.2 \text{ nAm} \pm 12.7 \text{ SD}$ ).

Finally, the group-level comparison of SEFs elicited by *Double* stimuli in *Dual* and in *Alone* disclosed a significant difference over left fronto-central sensors with a mean timeframe of 60–140 ms post-stimulus onset. A significant difference was also observed within a similar time window in 15 out of 16 subjects over the left fronto-central sensors. The cortical source responsible for this difference was accurately modeled by a single ECD at the left cSII cortex ( $[-42, -27, 25]$  mm) with significantly higher amplitude for SEFs elicited by *Double* stimuli in *Alone* than in *Dual* ( $36.4 \text{ nAm} \pm 18.1 \text{ SD}$  vs.  $16.9 \text{ nAm} \pm 9.9 \text{ SD}$ ).

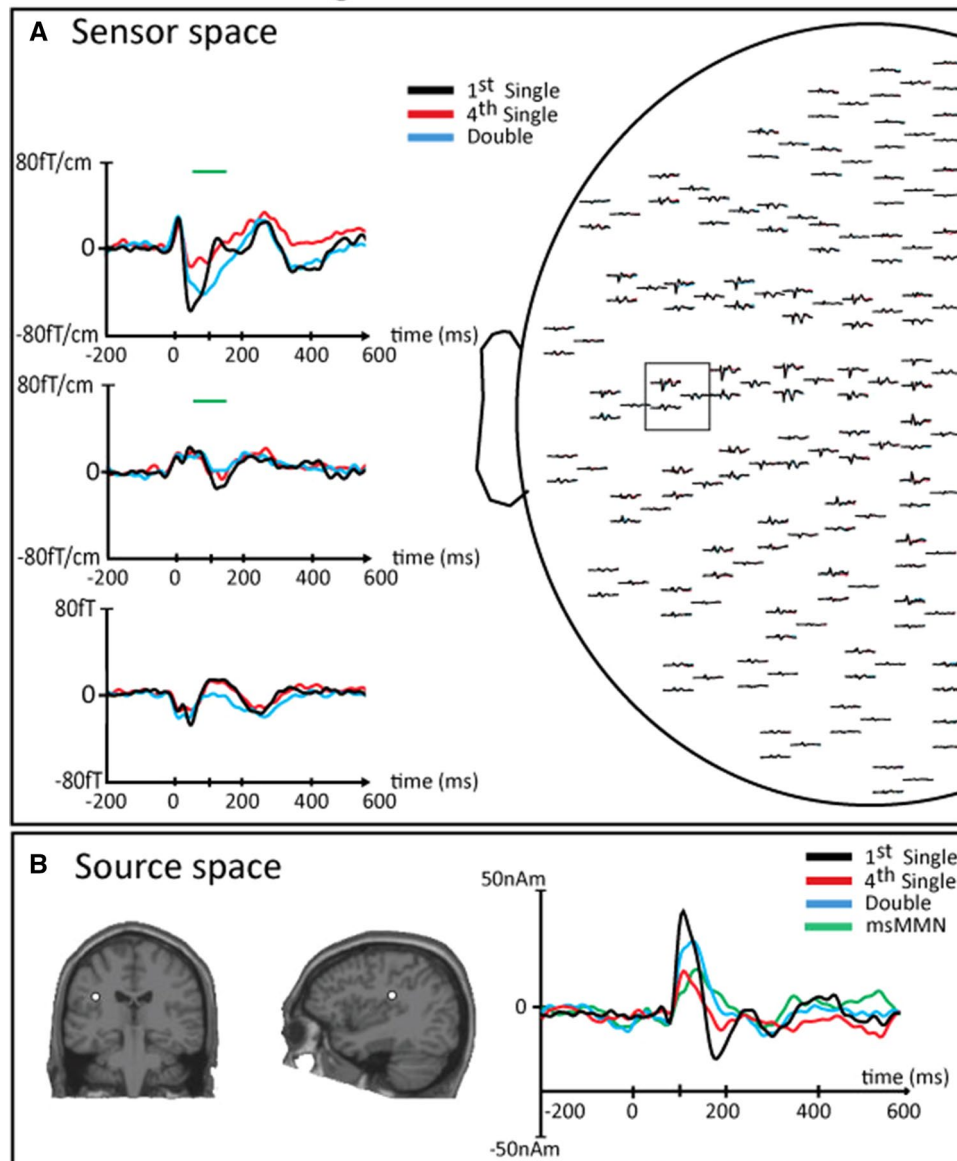
### Omission Condition (Fig. 6)

At the group level (Group B), *Omitted* stimuli did not lead to statistically significant difference in SEFs compared with *Single* stimuli. Subject-level statistics also failed to disclose any difference between *Omitted* and *Single* stimuli in eight out of ten subjects, while a significant difference between *Single* and *Omitted* stimuli was found over the left frontal sensors in two subjects with a mean timeframe of 80–166 ms post-omission onset with higher amplitude of cSII cortex responses for *Omitted* stimuli than for *Single* stimuli ( $19 \text{ nAm} \pm 5.6 \text{ SD}$  vs.  $2.6 \text{ nAm} \pm 1.3 \text{ SD}$ ).

## Discussion

Using a combination of different unilateral mechanical tactile paradigms, this MEG study brings novel empirical evidences suggesting that early tactile change detection is mainly processed within SII cortex contralateral to the stimulation with neural mechanisms in accordance with the predictive coding theory. Indeed, this study shows that, (1) in oddball paradigms, the predictability of deviant (i.e.,

## Long\_IBI\_Oddball



**Fig. 2** Grand-average results of the mismatch responses obtained at the sensor and the source levels for the *Long\_IBI\_Oddball* condition in subjects from group B. **a** Right. Left part of the MEG sensor array viewed from top. Left. Enlarged orthogonal planar gradiometers (Top, Middle) and magnetometer (Bottom) signals showing evoked magnetic responses corresponding to the first *Single* (black line), the fourth *Single* (red line) and *Double* (local deviants, blue line) stimuli of standard SSSSD blocks. Green lines indicate the timing of significant differences between *Single* and *Double* stimuli disclosed by non-parametric cluster-based statistics performed at the sensor level (planar gradiometers only). Of notice, in the sensor space, the polarity

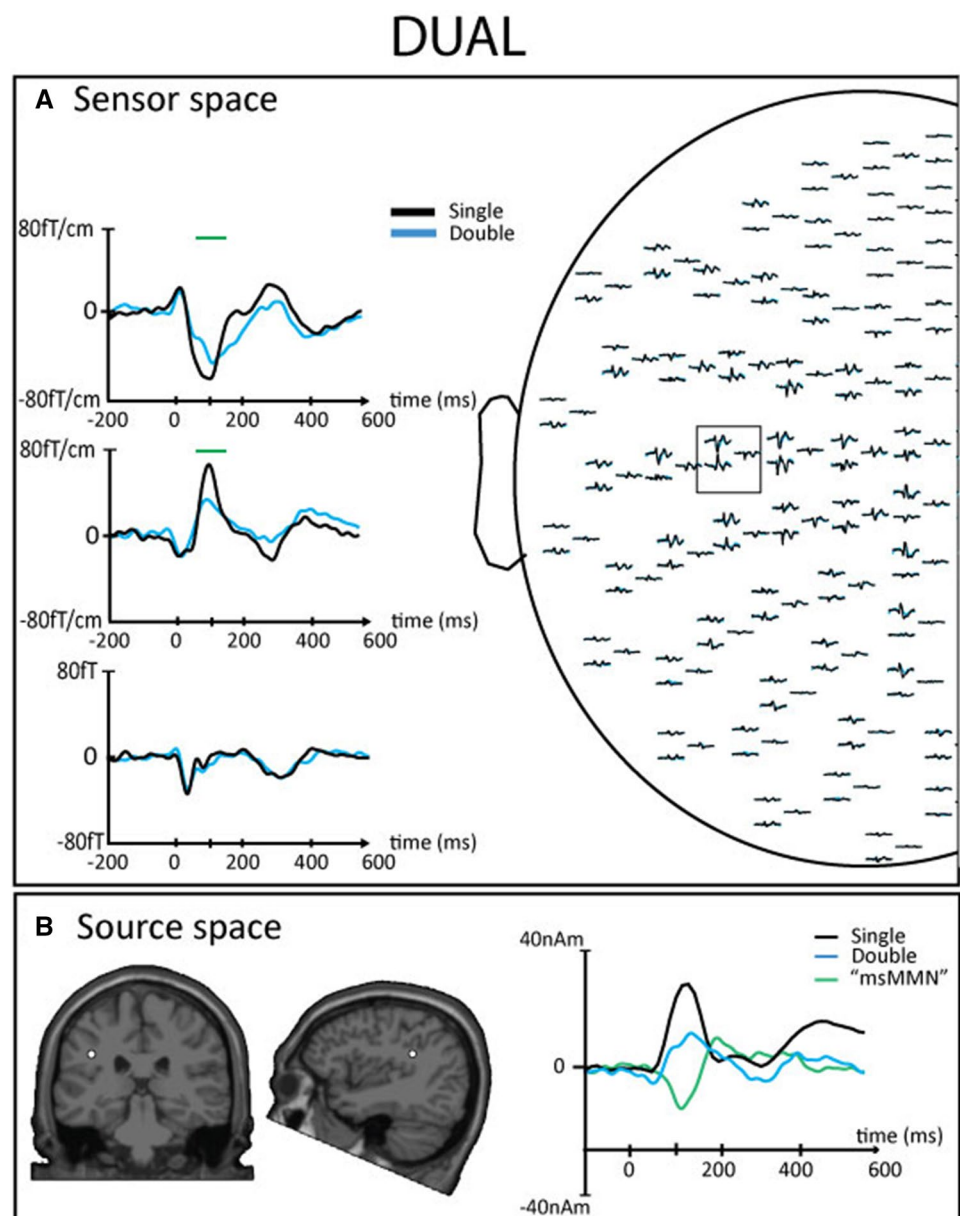
of the cortical responses may appear different from sensor to sensor due to different spatial sensitivity (i.e., lead field) of orthogonal planar gradiometers and magnetometers to right beneath or nearby neural sources. **b** Left. Coronal (left) and sagittal (right, left hemisphere) slices showing the location of the ECD (white dot; MNI coordinates:  $[-43, -19, 21]$  mm) that best explains the magnetic field pattern at the msMMN maximum amplitude. Right. Source waveforms corresponding to first *Single* (black line), fourth *Single* (red line), *Double* (local deviants, blue line) stimuli, and msMMN (green line) issued from the subtraction of the fourth *Single* stimulus from the *Double* stimuli

*Double*) stimuli occurrence modulates the amplitude of SII cortex msMMN responses, (2) SII cortex responses are attenuated after a first tactile stimulation even if the second stimulation is different from the first one, (3) *Omitted* stimuli

generate similar (or higher) SII cortex responses than tactile stimuli. These data suggest that the predictive coding framework can account for the SII cortex response features observed in this study.



**Fig. 3** Grand-average results of the responses obtained in the *Dual* condition for *Single* and *Double* stimuli at the sensor and the source levels in subjects from group A. **a** Results obtained at the sensor level. Please, refer to the legend of Fig. 2 for more information about this part of the figure. **b** Left. Coronal (left) and sagittal (right, left hemisphere) slices of the brain showing the location of the ECD (white dot; MNI coordinates: [−43, −27, 28] mm) that best explains the cortical generator of the “mismatch” response in *Dual*. Right. Source waveforms corresponding to *Single* stimuli (black line), *Double* stimuli (blue line) and “mismatch” response (green line). The “mismatch” response in *Dual* has an opposite polarity than in Fig. 2b, Right

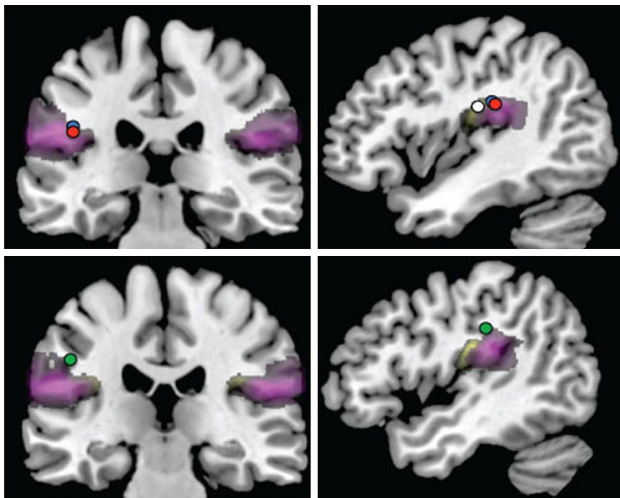


## SII Cortex is Involved in Early Tactile Change Detection

The cortical processing of sensory change detection is typically hierarchically organized and sequentially involves multiple levels of cortical areas (Downar et al. 2000; Bekinschtein et al. 2009; Chennu et al. 2013; Naeije et al. 2016). Indeed, modality specific “low-level” cortical areas are first involved in early change detection, which is followed by the recruitment of a “high-level” cortical network common to all sensory modalities and composed of fronto-parietal areas (Downar et al. 2000; Huang et al. 2005; Allen et al. 2016; Naeije et al. 2016). In this study, we found that the main modality specific “low-level” cortical area responsible for

early tactile change detection was within SII cortex contralateral to the tactile stimulation.

Group-level analyses disclosed significant differences between *Single* and *Double* stimuli in oddball (i.e., *Oddball* and *Long\_IBI\_Oddball*) and *Dual* conditions. At the group level, the cortical source responsible for the observed differences was localized at the left inferior parietal lobule. More precisely, group-level MNI coordinates corresponded to the first cytoarchitectonic subdivision of the parietal operculum (OP1) for *Dual*, the upper edge of OP1 for *Oddball* conditions, the edge between OP1 and the third cytoarchitectonic subdivision of the parietal operculum (OP3) for the *Long\_IBI\_Oddball* condition in the probabilistic maps of the human parietal operculum described Eickhoff et al. (2006,



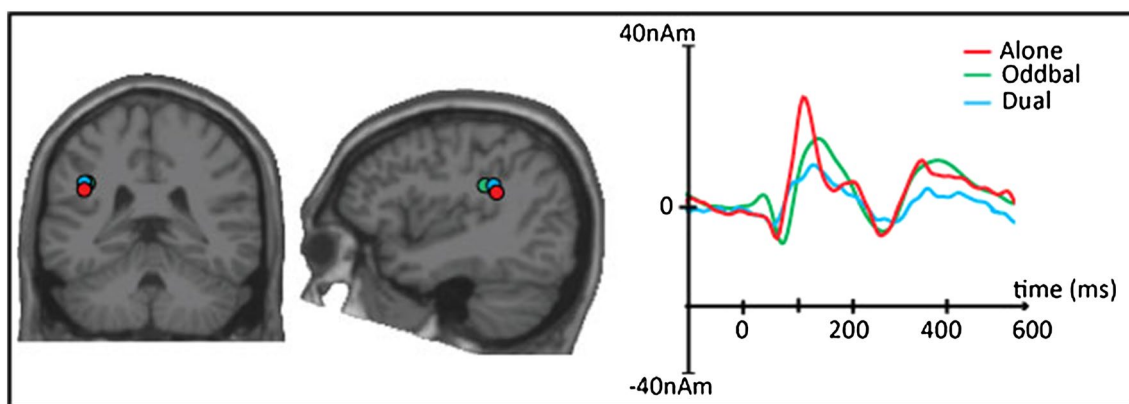
**Fig. 4** Responses obtained at the source level for the grand-averages of *Double* stimuli in the *Alone*, the *Dual* and the *Oddball* conditions in subjects from Group A. Left. Sagittal (left hemisphere) and coronal slices showing the location of the ECDs that best explain the cSII cortex response elicited by *Double* stimuli in *Alone* (red dot, MNI coordinates:  $[-42, -27, 25]$  mm), *Oddball* (green dot, MNI coordinates:  $[-47, -22, 35]$  mm) and *Dual* (blue dot, MNI coordinates:  $[-43, -27, 28]$  mm). Right. Source waveforms at the cSII cortex corresponding to *Double* stimuli in *Alone* (red line), *Oddball* (green line) and *Dual* (blue line) conditions. The source waveform displayed for the *Oddball* condition corresponds to those of the “Deviant” in Fig. 2 (left panel, Group-level msMMN) of Naeije et al. (2016)

2007). These group-level MNI coordinates are also close to those previously reported as SII cortex responses elicited by similar mechanical tactile stimuli in a previous MEG study (Hochstetter et al. 2001).

At the subject level, differences between *Single* and *Double* stimuli in oddball and *Dual* conditions were observed in about 75–80% of the subjects, which corresponds to the proportion of auditory mismatch responses observed in healthy adult subjects using similar local/global oddball paradigm (King et al. 2013). Of notice, the sMMN data available in the literature have mainly been reported at the group level, which renders the comparison with our subject-level results difficult to interpret (Kekoni et al. 1997; Shinozaki et al. 1998; Akatsuka et al. 2005; Restuccia et al. 2007; Spackman et al. 2007; Butler et al. 2012; Strömmer et al. 2014).

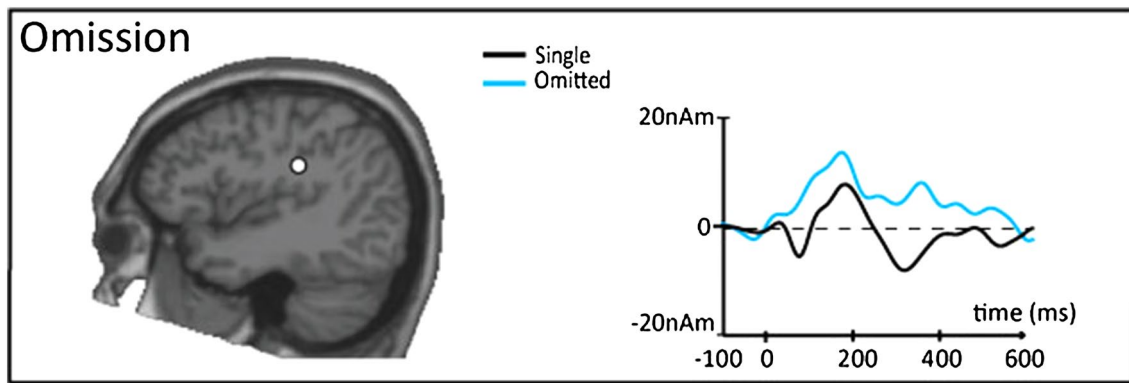
Early tactile change detection processing could have occurred in uni-modal areas within SI or SII cortices. The timing of cortical activity highlighted in this study concurs with the timing during which SII cortex is mainly activated as demonstrated by previous MEG somatosensory studies (Hari et al. 1993; Mauguiere et al. 1997). Furthermore, no statistically significant difference was found at the timeframe of early SI cortex response. While SI cortex reactivation is known to occur later in the somatosensory processing (Bradley et al. 2016), the present data suggest that either such reactivation phenomenon was not different between *Single* and *Double* stimuli, or that this effect was minor as the cortical responses accounting for early tactile change detection were accurately modelled by only one single dipole located at cSII cortex.

While the cortical generator responsible for the differences observed between the oddball and *Dual* conditions was located at cSII cortex at the group level (and in each subject) as was the cortical generator responsible for the difference between *Single* and *Omitted* stimuli observed in two subjects, the timing of significant differences differed



**Fig. 5** Superposition of the four dipoles obtained in the different conditions on the probabilistic maps of the first cytoarchitectonic subdivision of the parietal operculum (OP1, in purple) and the third cytoarchitectonic subdivision of the parietal operculum (OP3, in yellow) described by Eickhoff et al. (2006, 2007) as provided by SPM Anatomy ([http://www.fzjuelich.de/inm/inm1/DE/Forschung/\\_docs/SPMAnatomyToolbox/SPMAnatomyToolbox\\_node.html](http://www.fzjuelich.de/inm/inm1/DE/Forschung/_docs/SPMAnatomyToolbox/SPMAnatomyToolbox_node.html)); Coronal

(left) and sagittal (right, left hemisphere) slices of the brain showing the location of the ECDs that best explained the cSII response elicited by *Double* stimuli in *Alone* (red dot, MNI coordinates:  $[-42, -27, 25]$  mm), *Oddball* (green dot, MNI coordinates:  $[-47, -22, 35]$  mm), *Dual* (blue dot, MNI coordinates:  $[-43, -27, 28]$  mm) and *Long\_IBI\_Oddball* (white dot; MNI coordinates:  $[-43, -19, 21]$  mm)



**Fig. 6** Responses obtained at the source level for the grand-averages of the *Omission* conditions in subjects group B. Left. Sagittal slices of the left hemisphere showing the location of the ECD (white dot, MNI coordinates: [−46, −18, 24] mm) that best explains, at the group

level, the cSII cortex responses elicited by *Omitted* stimuli. Right. Source waveforms at cSII cortex corresponding to *Single* (black line) and *Omitted* (blue line) stimuli

between the conditions. Indeed, the comparisons involving *Double* stimuli not inserted in classical oddball conditions (i.e., *Dual*) led to significant differences over longer timeframes and responses to omissions displayed longer and delayed timeframes of activation compared with *Double* stimuli. These results are in line with the literature. Indeed, previous studies have shown that “deviant” stimuli not embedded in a stream of standards actually generate higher amplitude evoked fields with slightly delayed latencies (Hari et al. 1993; Kekoni et al. 1997) resulting in differences with standards for longer time-periods. In addition, other studies have shown that the absence of expected stimuli like in the *Omission* condition or in *off*-responses also leads to delayed responses compared to deviant stimuli with increased latency ranging from 25 ms in somatosensory *off*-responses (Yamashiro et al. 2009) to about 50 ms in the auditory modality (Wacongne et al. 2011; Chennu et al. 2016). This might therefore explain the different timeframe of responses observed in this study for the *Omission* condition.

Previous oddball studies investigating the brain responses elicited by somatosensory change detection used electrical (Kida et al. 2001, 2012) or vibratory (Kekoni et al. 1997; Spackman et al. 2007) stimuli. In the present study, we used a more ordinary mechanical stimulation and chose to apply the stimulation on the same finger to recruit as much as possible common peripheral and cortical pathways between different tactile stimuli. In oddball paradigms (*Oddball* and *Long\_IBI\_Oddball*), the increased amplitude response at SII cortex for deviants (i.e., *Double* stimuli) compared with standards (i.e., *Single* stimuli) was not related to differences in the physical characteristics of the stimuli (i.e., a higher amount of skin mechanoreceptors was stimulated for deviants than for standards) since we have previously shown that flipping standard and deviant stimuli disclosed similar msMMN at cSII cortex (Naeije et al. 2016). Furthermore,

the smaller amplitude of cSII cortex responses elicited by *Double* stimuli after one *Single* stimulus observed in the *Dual* condition do not support that hypothesis. These data highlight the main role of cSII cortex in early tactile change detection and concur with a previous MEG study, which found that SII cortex is involved in sMMN responses (Akatsuka et al. 2007). In addition, functional magnetic resonance imaging (fMRI) studies demonstrated that SII cortex is selectively activated for spatial deviants compared with standards (Chen et al. 2008) and is the only modality-specific cortical area responsive to somatosensory deviants in uni- and multimodal sensory oddball paradigms (Downar et al. 2000). Also, one EEG study showed that this cortical area is prominently sensitive to the surprising aspects of tactile stimuli (Ostwald et al. 2012).

SII cortex is known to process the complex features of somatosensory stimuli such as space location (Zhu, et al. 2007), laterality (Simoes et al. 2002), self perception of body scheme (Avikainen et al. 2002), intensity (Otsuru et al. 2011) and pain (Chen et al. 2008). Finally, MEG (Hämäläinen et al. 2002) and fMRI (Fujiwara et al. 2002) studies also pointed at the role of SII cortex in selective somatosensory attention. These integrative features of SII cortex for somatosensory processing support cSII cortex as one of the key brain areas for early tactile change detection.

#### Attenuation of cSII Cortex Responses by Successive Tactile Stimuli and the Role of Adaptation in sMMN Genesis

In the *Long\_IBI\_Oddball* condition, we observed a significant attenuation of cSII cortex responses between the first and the fourth *Single* stimuli of standard SSSSD blocks. By contrast, this effect was not significant at the group level in the *Oddball* condition. These findings are in line with a

previous MEG study that used sequences of identical pneumatic tactile stimuli and which disclosed substantial attenuation of SII cortex responses after the first tactile stimulus (Popescu et al. 2013). They also concur with studies that assessed the effect of ISI on SEFs, which showed a substantial decrease in SII cortex responses when ISI was constant and inferior to 1 s, such as between the first and the following three standards in both oddball conditions (Allison 1962; Wikström et al. 1996; Mauguier et al. 1997). Indeed, in the *Oddball* condition, the IBI was constant and set at 0.8 s, while in *Long\_IBI\_Oddball*, it was randomly set between 1.5 and 2.5 s, which explains why cSII response to the first standard (i.e., *Single* stimulus) in *Long\_IBI\_Oddball* was higher than for the subsequent ones. Furthermore, in the *Dual* condition, we observed a decrease in SEFs amplitude elicited by *Double* stimuli at cSII cortex after one *Single* stimulus, despite the fact that a larger skin surface was stimulated in *Double* than in *Single* stimuli. This finding might be related to a repetition suppression of shared feature specific neurons at SII cortex and the existence of an important overlap in fingers representation (i.e., receptive fields) within this brain area (Hoechstetter et al. 2001; Ruben et al. 2001). Finally, *Double* stimuli elicited higher SII cortex responses in the *Alone* than in the *Dual* condition. Taken together, those data support the existence of a substantial adaptation/attenuation phenomenon at cSII cortex after a first tactile finger stimulation; the second one being either a similar or even a different tactile stimulus on the same finger. Still, such phenomenon actually fails to explain why, after four *Single* stimuli in oddball conditions, *Double* stimuli display higher cortical responses compared to the fourth *Single* stimulus. They also do not explain why *Double* stimuli elicit higher SEFs amplitude in *Oddball* than in *Dual*. Indeed, if only the adaptation mechanism would be involved in the sMMN genesis and considering the high degree of overlap in the fingers' receptive fields at SII cortex, *Double* stimuli should elicit similar or attenuated cSII cortex responses after *Single* stimuli in *Dual* and oddball conditions.

These results therefore suggest that other mechanisms than the adaptation phenomenon accounts for the smMMN observed at cSII cortex in oddball conditions.

### SII Cortex Detects Early Tactile Change Under the Predictive Coding Framework

As a whole, the results of this study give novel empirical evidence supporting the involvement of the predictive coding in early tactile change detection.

First, the predictive coding framework can account for the observation that *Double* stimuli elicit a typical sMMN (i.e., amplitude of evoked responses to *Double* stimuli > to *Single* stimuli) when they occurred as deviants in sequences of four *Single* stimuli while they elicited a “mismatch” response of

opposite polarity at cSII cortex when they occurred after one *Single* stimulus in the *Dual* condition (i.e., amplitude of evoked responses to *Double* stimuli < to *Single* stimuli). Indeed, based on these findings, we postulate that in the *Dual* condition, predictions of potential upcoming sensory stimuli are dominated by sensory modality predictions (i.e., predictions of future sensory inputs are based on/dominated by the sensory modality of the former sensory input). By contrast, in the oddball conditions, we hypothesize that the memory trace of repetitive somatosensory stimuli progressively refines predictions that become dominated by specific features (e.g., submodality, timing, intensity, spatial location, etc.) of somatosensory stimuli (i.e., predictions become based on/are refined by a learned regularity of sensory inputs). According to this hypothesis, *Double* stimuli in the *Dual* condition would not represent a prediction error and the response to the *Double* stimuli in *Dual* may be considered as a repetition attenuation/suppression. On the other hand, the *Double* stimuli in *Oddball* represents an error of prediction upon the specific features of the stimuli and lead to increased response at cSII cortex compared to *Single* stimuli, which would be in agreement with the *model adjustment* theory.

Second, further arguments supporting the predictive coding theory come from the observed modulation of SII cortex response amplitude by the predictability of deviant occurrence. Indeed, we demonstrate in the *Oddball* condition that the amplitude of the smMMN was higher when the predictability of experiencing deviant (i.e., *Double*) stimuli was lessened by the random insertion of deviant blocks (SSSS blocks), i.e., when the predictability of local deviant occurrence was more difficult to infer from previous experiences. Such tuning of MMN responses by the predictability of deviants occurrence has already been described for the auditory modality in previous MEG studies. It indeed accounts for the differential neural adaptation to expected or unexpected repetitions of auditory stimuli in the auditory cortex (i.e., less adaptation when repetitions are unexpected) (Todorovic et al. 2011) and for increased auditory MMN responses when deviants are not/less predictable (Wacongne et al. 2011). Modulation of SII cortex responses by predictions based on memory traces of former identical or repetitive somatosensory stimuli could also explain why SII cortex responses elicited by a change in the electrical intensity of somatosensory stimuli are increased when longer preceding conditioning stimuli are applied (Otsuru et al. 2011).

Third, the *Omission* condition provides additional evidences supporting a predictive coding mechanism for SII cortex responses to tactile change detection. Indeed, under the predictive coding framework, *Omitted* stimuli embedded in repetitive sequences of stimuli might correspond to a prediction error and should therefore lead to cortical response, while they should not elicit any cortical response under the

*adaptation/adjustment/rate effect* theories (Wacongne et al. 2011). In this study, we found that *Omitted* stimuli elicited cortical responses that were similar (or even higher in two subjects) in amplitude than responses to *Single* stimuli. The cortical responses to *Omitted* stimuli argue in favor of both the predictive coding theory and the hypothesis that SII cortex is the cortical region where tactile prediction errors are mainly processed. These results are in line with a previous MEG study that found SII cortex to be activated by “off-responses” (i.e., when somatosensory stimuli abruptly stop) (Yamashiro et al. 2009; Otsuru et al. 2011).

Finally, this framework can also explain the effect of the IBI manipulation (or ISI in classic studies assessing the effect of ISI on SEFs (Allison 1962; Wikström et al. 1996; Mauguier et al. 1997) on SII cortex responses. Indeed, according to the predictive coding theory, somatosensory novelty detection responses should be affected by previous sensory experiences. In long and random IBI conditions, the occurrence of novel incoming stimulations are less predictable and the saliency (or surprise) of novel somatosensory stimuli therefore increases leading to higher SII cortex responses, such as for the first *Single* stimulus of SSSSD blocks in *Long\_IBI\_oddball*. The predictive coding framework could also account for the observation that response at SII cortex to random stimuli continue to progressively increase for ISI ranging from 1 to 5 s (Wikström et al. 1996) and even up to 8 s in selected individuals (Hari et al. 1993). Indeed, based on this theory, it can be considered that the longer the ISI is, the less predictable the next sensory stimulus becomes. Ultimately, this framework could also explain why, at the group level, cSII cortex responses to *Double* stimuli were significantly higher in the *Alone* than in the *Dual* or the *Oddball* conditions due to a longer interval between the tactile stimuli. Indeed, in such *Alone* paradigm, the “surprise” or the difficulty to predict the occurrence of the next stimulus reach their maximum and therefore lead to cSII cortex response with the highest amplitude.

## Conclusions

By integrating the cortical responses obtained in different unilateral mechanical tactile paradigms, this MEG study provides novel empirical evidence supporting that early tactile change detection involves mainly cSII cortex with cortical responses consistent with the predictive coding framework.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

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