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ORIGINAL ARTICLE

Auditory change-related cortical response is associated with hypervigilance to pain in healthy volunteers

Naofumi Otsuru[1,2] | **Mayu Ogawa**[2] | **Hirotake Yokota**[1,2] | **Shota Miyaguchi**[1,2] | **Sho Kojima**[1,2] | **Kei Saito**[1,2] | **Yasuto Inukai**[1,2] | **Hideaki Onishi**[1,2]

[1]Institute for Human Movement and Medical Sciences, Niigata University of Health and Welfare, Niigata, Japan

[2]Department of Physical Therapy, Faculty of Rehabilitation, Niigata University of Health and Welfare, Niigata, Japan

Correspondence
Naofumi Otsuru, Institute for Human Movement and Medical Sciences, Niigata University of Health and Welfare, 1398 Shimami-Cho, Kita-Ku, Niigata 950-3198, Japan.
Email: otsuru@nuhw.ac.jp

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Abstract

Background: Patients with chronic pain exhibit hypervigilance (heightened responsiveness to stimuli) to innocuous auditory stimuli as well as noxious stimuli. "Generalized hypervigilance" suggests that individuals who show heightened responsiveness to one sensory system also show hypervigilance to other modalities. However, research exploring the existence of generalized hypervigilance in healthy subjects is limited.

Methods: We investigated whether hypervigilance to pain is associated with auditory stimuli in healthy subjects using the pain vigilance and awareness questionnaire (PVAQ) and auditory change-related cortical responses (ACRs). ACRs are thought to reflect a change detection system, based on preceding sensory memory. We recorded ACRs under conditions that varied in terms of the accumulation of sensory memory as follows: short-ACR, with short preceding continuous stimuli and long-ACR, with long preceding continuous stimuli. In addition, the attention to pain (PVAQ-AP) and attention to changes in pain (PVAQ-ACP) subscales were evaluated.

Results: Amplitudes of long-ACR showed significant positive correlations with PVAQ-ACP, whereas those of short-ACR did not show any significant correlations.

Conclusions: Generalized hypervigilance may be observed even in healthy subjects. ACR may be a useful index to evaluate the hypervigilance state in the human brain.

1 | INTRODUCTION

Previous studies have shown that hypervigilance, which is higher-than-normal responsiveness to external stimuli, is observed in patients with chronic pain. Hypervigilance has been confirmed not only for noxious stimuli (Berglund et al., 2002; Desmeules et al., 2003) but also for innocuous somatosensory stimuli, including warm or tactile ones (Geisser et al., 2003; Hollins et al., 2009; Montoya et al., 2006), and even for auditory stimuli, in fibromyalgia patients (Carrillo-De-La-Pena et al., 2006; Geisser et al., 2008; Hollins et al., 2009; McDermid et al., 1996). For example, patients with fibromyalgia reported auditory stimuli as louder and more unpleasant (Hollins et al., 2009) and showed steeper increases in the amplitude of auditory evoked potentials with increasing stimulus intensity than did healthy

controls (Carrillo-De-La-Pena et al., 2006). These studies revealed that, when hypervigilant to pain, fibromyalgia patients feel that non-painful auditory stimuli are also more salient. This indicates that the saliency detection system is shared among sensory modalities; this is called generalized hypervigilance (Chapman, 1978; McDermid et al., 1996; Roelofs et al., 2003). If true, then even in healthy participants, individuals who are hypervigilant to pain could also have hypervigilance to auditory stimuli.

To investigate individual hypervigilance to auditory stimuli, the auditory change-related cortical response (ACR) is suitable. The ACR can be elicited by various abrupt changes in stimuli, including the sound's intensity, frequency and location, following a preceding continuous state, and peaks at approximately 100–130 ms after the onset of the change (Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010; Nakagawa et al., 2014; Nishihara et al., 2011; Tanahashi et al., 2016; Yamashiro et al., 2009, 2011). ACRs have good test–retest reliability (Inui et al., 2012; Otsuru et al., 2012). The ACR has the following characteristics. First, the ACR can be elicited without paying attention to auditory stimuli, and its amplitude reflects the magnitude of the auditory change irrespective of the physical sound intensity (Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010; Inui, Urakawa, Yamashiro, Otsuru, Takeshima, et al., 2010; Nishihara et al., 2011; Yamashiro et al., 2011); that is, the ACR is considered as an automatic, pre-attentive salience detection response. Second, the amplitude of the ACR is larger when the preceding continuous state (repetitive presentation of identical stimuli) is longer (Akiyama et al., 2011; Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010; Inui, Urakawa, Yamashiro, Otsuru, Takeshima, et al., 2010; Yamashiro et al., 2011) and is attenuated when the preceding continuous state is broken with a weak stimulus (Inui et al., 2012, 2016). This indicates that the ACR is involved in accumulation of predictable states (preceding sensory memory). Based on these earlier findings, the ACR should purely reflect salience detection (hypervigilance) to auditory signals, based on the preceding continuous state. To measure hypervigilance to pain, the pain vigilance and awareness questionnaire (PVAQ) is widely used (McCracken, 1997). Compared with healthy (i.e., pain-free) subjects, it has been shown that PVAQ scores are higher in chronic pain patients (Daenen et al., 2013; van Aken et al., 2017; Van Damme et al., 2015; Vossen et al., 2018). Moreover, even in healthy subjects, the PVAQ is closely related to pain sensitivity (Baum et al., 2011; Roelofs et al., 2004).

In the present study, we hypothesized that subjects with hypervigilance to pain have high sensitivity to auditory change. Thus, we investigated the relationship between the PVAQ and the amplitude of the ACR. The ACR was recorded in two conditions that differ in terms of accumulation of sensory memory (short or long continuous preceding state). Moreover, to investigate whether the ACR is specifically related to hypervigilance to pain, we investigated the relationship between the ACR and the state-trait anxiety inventory (STAI), which is another measure of psychological hypervigilance.

2 | METHODS

2.1 | Participants

Twenty-five healthy participants (nine women and 16 men; mean age: 22.0 ± 0.1 years) were recruited from the Niigata University of Health and Welfare. None had a history of any neurological disorder, and none took any medications before the experiment. All subjects had normal hearing by self-report. Written informed consent was obtained from each participant before the study, which was approved by the ethics committee at Niigata University of Health and Welfare.

2.2 | Auditory stimuli

To record the ACR, we used a train of brief tone pulses (Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010; Yamashiro et al., 2009). By using a train of brief tone pulses, we could create an abruptly changing tone stimulus without any undesired edge. The tone frequency was 800 Hz, and the duration was 25 ms (5-ms rise and fall times); that is, for example, a 100-ms train comprising four tones. The change sound to elicit the ACR was a 100-ms train at 75 dB. In the short continuous condition, the change sound was presented following a 100-ms pulse train at 70 dB (short-change trial). The control sound was a 200-ms train at 70 dB without a change (short-control trial). In the long continuous condition, the change sound was presented following a 500-ms train at 70 dB (long-change trial). The control sound was a 600-ms train at 70 dB without change (long-control trial; Figure 1). Note that the change sound was identical in both conditions, but the length of the preceding continuous state (accumulation of sensory memory) was different.

2.3 | Electroencephalographic recordings

The experiment was carried out in a shielded room (Tokin Ltd). Participants sat in a comfortable reclining chair with a mounted headrest. They were instructed to watch a silent movie and to not attend to the auditory stimuli.

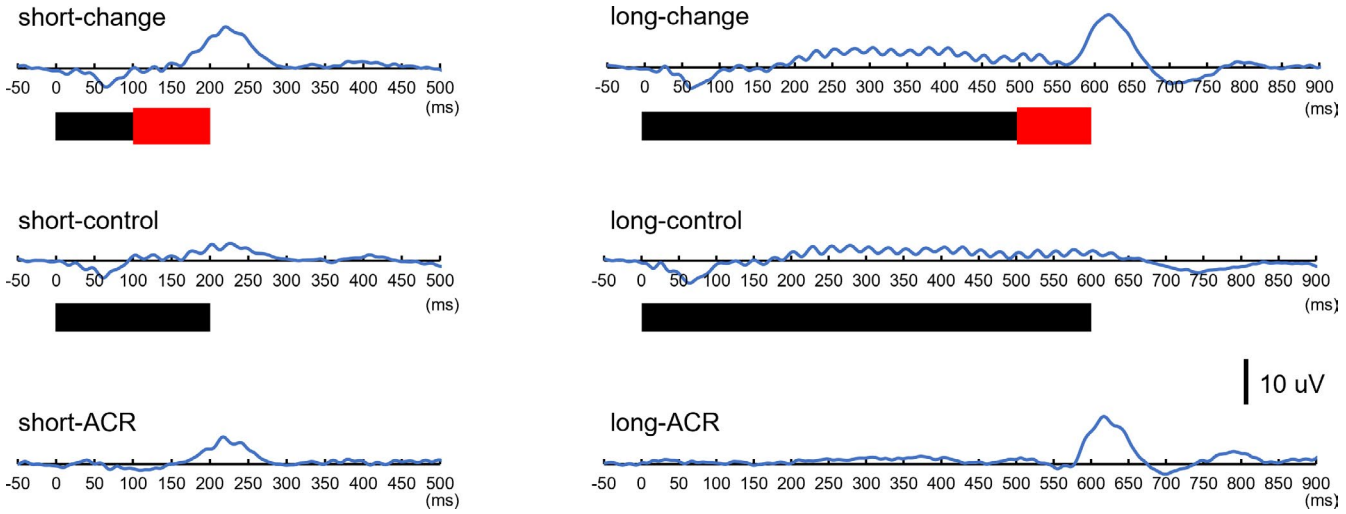

FIGURE 1 Grand-averaged waveforms and trains of auditory stimuli in each trial. Black rectangles represent the trains of brief tone pulses at 70 dB and red rectangles represent the change sound, which was a train of brief tone pulses at 75 dB. Note that a clear auditory change-related cortical response (ACR) was elicited only in the change trials. The waveforms of short- and long-ACRs (bottom) are obtained by subtracting the control waveform (middle trace) from the change waveform (upper trace) in each trial

Electroencephalographic signals were recorded from the Fz electrode, referenced to linked mastoids (P9–P10), of the 10–10 system. It has been confirmed previously that this layout is suitable for recording the ACR (Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010). The impedances for all electrodes were below 5 kΩ. The responses were recorded with a 0.5–100-Hz bandpass filter, at a sampling rate of 1000 Hz. In each condition, the two trains (change and control trials) were presented with equal probability but at random, with an inter-trial interval of 300 ms. Sound stimuli were presented binaurally through a plastic tube and earpieces (E-A-RTone 3A; Aero Company). The order of the two conditions (short and long continuous conditions) was randomized among subjects. Approximately 100 trials without artefacts were averaged for each train. The period of analysis was from 50 ms before the start of the train to 400 ms after the onset of the change sound. An offline low-pass filter of 40 Hz was applied. We used the period of 50 ms before the start of each train as the baseline. After each averaged waveform was obtained, to extract the ACR, the difference waveform in each condition (short- and long-ACR) was calculated by subtracting the averaged waveform for control trials from that for change trials (Figure 1). Using the difference waveforms, amplitudes of the ACR were determined as the maximum amplitude between 80 and 180 ms after the onset of the change sound.

2.4 | Questionnaires

The PVAQ is a measure of hypervigilance to pain (McCracken, 1997) and contains 16 items (e.g., "I am very sensitive to pain" and "I am quick to notice changes in pain intensity") rated from 0 (never) to 5 (always) on 6-point scale. It comprises two subscales that measure attention to pain (PVAQ-AP: ranging from 0 to 50) and attention to changes in pain (PVAQ-ACP: ranging from 0 and 30; Roelofs et al., 2003). Participants completed the Japanese version of the PVAQ, which has good internal consistency (Cronbach's $\alpha = 0.89$ for the PVAQ-AP and 0.81 for the PVAQ-ACP; Imai et al., 2009).

The STAI is a measure of anxiety with two subscales. The state anxiety subscale (STAI-S) evaluates the current state of anxiety, and the trait anxiety subscale (STAI-T) evaluates generalized propensity to be anxious (Spielberger, 1983). Each subscale contains 20 items on 4-point scale (range from 20 to 80). Higher scores indicate more anxiety. We used the Japanese version of the STAI, which has good internal consistency (Cronbach's $\alpha = 0.911$ for the STAI-S and 0.904 for the STAI-T; Iwata et al., 2000).

2.5 | Analysis

We first used the Shapiro–Wilk test to check normality of the data. The test revealed that the PVAQ-ACP was not normally distributed ($p = 0.004$). Spearman's correlation analysis was carried out to detect associations between all variables (i.e., the amplitudes of short- and long-ACRs, PVAQ-AP, PVAQ-ACP, STAI-S and STAI-T). Bonferroni's correction was used for multiple correlation tests. We used a paired-t test to compare amplitudes between the short- and long-ACRs. In all statistical analyses, $p < 0.05$ was considered statistically

significant. Data are expressed as means ± standard errors.

3 | RESULTS

Two subjects were excluded from the analysis because a clear short-ACR could not be recorded. As shown in Figure 1, clear ACRs were elicited around 125 ms after the change sound was presented (129.4 ± 4.0 ms for the short-ACR and 122.9 ± 2.7 ms for the long-ACR). The paired-*t* test revealed that the amplitude of the long-ACR (10.9 ± 0.7 μV) was significantly larger than that of the short-ACR (6.7 ± 0.5 μV; $p < 0.001$).

As shown in Table 1 and Figure 2, the amplitude of the long-ACR was significantly positively correlated with the PVAQ-ACP ($r = 0.65$, $p = 0.001$) and PVAQ-AP ($r = 0.42$, $p = 0.045$). The former correlation remained significant after Bonferroni's correction ($p = 0.012$). There were no significant correlations between the amplitude of the short-ACR and any of the other variables.

4 | DISCUSSION

In the present study, we confirmed that the amplitude of the long-ACR was significantly larger than that of the short-ACR, as reported previously (Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010). The result is consistent with previous findings that the ACR is involved in accumulation of predictable state (preceding sensory memory). In addition, the amplitude of the long-ACR showed a significant positive correlation with the PVAQ-ACP, which suggested that generalized hypervigilance also exists in healthy subjects. These results indicate that the ACR reflects individual pain hypervigilance and may be a useful index to evaluate the hypervigilance state in the human brain.

In patients with chronic pain, hypervigilance to pain is observed (Berglund et al., 2002; Desmeules et al., 2003) as well as hypervigilance to auditory stimuli (Carrillo-De-La-Pena et al., 2006; Geisser et al., 2008; Hollins et al., 2009). This is called generalized hypervigilance. In the present study, we assessed hypervigilance to pain using the PVAQ, which has been shown to relate to high pain sensitivity (Baum et al., 2011; Roelofs et al., 2004) in healthy subjects. Our results showed that the PVAQ-ACP was significantly correlated with the amplitude of the long-ACR, which suggested that generalized hypervigilance also exists in healthy subjects. The ACR has been shown to reflect a change detection system that is based on sensory memory (Akiyama et al., 2011; Inui et al., 2012, 2016; Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010; Inui, Urakawa, Yamashiro,

TABLE 1 Relationships between amplitude of the auditory change-related cortical responses (ACR) and psychometric questionnaire scores

Variables	Amplitude of the short-ACR	Amplitude of the long-ACR	STAI-S	STAI-T	PVAQ-AP
Amplitude of the long-ACR					
r	0.273				
p-value	0.208				
STAI-S					
r	0.357	0.299			
p-value	0.095	0.166			
STAI-T					
r	0.012	0.225	0.294		
p-value	0.957	0.303	0.173		
PVAQ-AP					
r	−0.092	0.421[a]	0.073	0.383	
p-value	0.676	0.045	0.741	0.072	
PVAQ-ACP					
r	0.158	0.647[b]	0.348	0.328	0.720[b]
p-value	0.472	0.001	0.104	0.127	0.0001

Abbreviations: PVAQ-ACP, PVAQ subscale regarding attention to changes in pain; PVAQ-AP, pain vigilance and awareness questionnaire (PVAQ) subscale regarding attention to pain; STAI-S, state-trait anxiety inventory (STAI) subscale regarding current state of anxiety; STAI-T, STAI subscale regarding generalized propensity to anxiety. P-values are shown as uncorrected values.

[a]Statistically significant ($p < 0.05$) before Bonferroni's correction.

[b]Statistically significant ($p < 0.003$) after Bonferroni's correction.

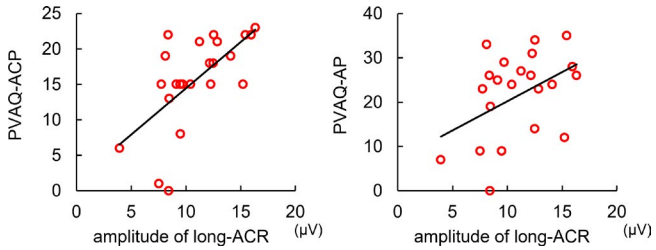

FIGURE 2 Relationships between the PVAQ-ACP, PVAQ-AP and amplitudes of the long-ACR. PVAQ-ACP, pain vigilance and awareness questionnaire (PVAQ) subscale for attention to changes in pain; PVAQ-AP, PVAQ subscale for attention to pain

Otsuru, Takeshima, et al., 2010; Nakagawa et al., 2014; Nishihara et al., 2011, 2014; Otsuru et al., 2012; Tanahashi et al., 2016; Yamashiro et al., 2009, 2011). As replicated in the present study (Figure 1), one of the important features of ACR is that a larger amplitude is elicited when the preceding continuous state is longer. That is, the ACR is not dependent on peripheral input, but on sensory memory. It has been shown that amplitude is increased in proportion to the logarithm of the length of the preceding continuous state (Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010; Yamashiro et al., 2011), and the length of the preceding stimulus of 500 ms was shown to be of sufficient duration to form adequate sensory memory to elicit the ACR (Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010). Taken together, hypervigilance to pain appears to be associated with the responsiveness to auditory change based on sensory memory. In line with our findings, a previous study showed that the ACR amplitude is significantly correlated with harm-avoidance temperament (Tanahashi et al., 2016), which is associated with pain-related anxiety in chronic pain patients (Knaster et al., 2012) and pain perception in healthy volunteers (Pud et al., 2004). These studies support the notion that the ACR reflects generalized hypervigilance.

Similar to the ACR, the mismatch negativity (MMN) is a well-established cortical response that reflects pre-attentive salience detection processing (Näätänen et al., 2007). To our knowledge, there has not been any study investigating the direct relationship between the PVAQ and MMN. However, there have been some studies investigating the MMN in chronic pain patients (Choi et al., 2015; Dick et al., 2003; Fan et al., 2018; Yao et al., 2011). Two studies demonstrated that chronic pain patients have decreased amplitude of the MMN (Choi et al., 2015; Fan et al., 2018), whereas one study showed no difference (Yao et al., 2011). MMN amplitude was also decreased when healthy subjects were exposed to acute pain and was increased when chronic pain patients were given an analgesic nerve block treatment (Dick et al., 2003). Together, these studies show that pain leads to decreased auditory hypervigilance. Evaluations of the MMN support the conclusion that the pain and auditory systems share the same resource for hypervigilance.

The current results should be interpreted in light of several limitations. Because we recruited only young healthy volunteers, it is not clear whether the relationships observed in the present study apply to older subjects or patients with pain or anxiety. In fact, the mean values for PVAQ-AP and ACP were higher in patients with chronic postsurgical pain (29.5 and 23.7, respectively; Gupta et al., 2020) and chronic orofacial pain (25.3 and 24.2, respectively; Forssell et al., 2020) than those observed in the young healthy volunteers in the present study (21.4 and 15.7, respectively). The lower value distribution observed in young healthy volunteers may have affected the relationship between PVAQ and ACR. This requires clarification in future studies in pain patients. Additionally, we could not identify the cortical sources of the ACR because we recorded in only a limited number of electrodes. However, numerous previous studies have demonstrated that the source of the ACR is the superior temporal gyrus (Akiyama et al., 2011; Inui et al., 2012, 2016; Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010; Inui, Urakawa, Yamashiro, Otsuru, Takeshima, et al., 2010; Motomura et al., 2019; Nakagawa et al., 2014; Nishihara et al., 2014; Otsuru et al., 2012; Yamashiro et al., 2009, 2011), and the recording montage we used is considered suitable for detecting the ACR (Inui, Urakawa, Yamashiro, Otsuru, Nishihara, et al., 2010). Finally, in the present study, we investigated the ACR only at around 120 ms after the onset of change and not the earlier component (P50), which is also involved in the ACR (Nakagawa et al., 2014). Whether the early component is related to hypervigilance to pain needs to be clarified in the future.

In conclusion, we found that the amplitude of the ACR is significantly correlated with the PVAQ-ACP. Therefore, the ACR could be used as an index for hypervigilance to pain. In the future, we plan to investigate the relationship between the ACR and psychological hypervigilance in patients with chronic pain to demonstrate the utility of the ACR.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

Conceptualization of study: N.O.; data collection and preparation: N.O., M.O.; data analysis: N.O., M.O.; data interpretation: N.O., M.O., H.Y., S.M., S.K., K.S., Y.I., H.O.; manuscript preparation: N.O., M.O., H.O. All authors discussed the results and commented on the manuscript.

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