Anticipation process of the human brain measured by stimulus-preceding negativity (SPN)

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Abstract The human brain is activated even before a stimulus occurs if a person knows the stimulus will happen within a few seconds. The neural basis for this cognitive function, termed anticipation, is the subject of this review. One method for investigating the brain mechanism of anticipation employs stimulus-preceding negativity (SPN), which is a type of event-related potential (ERP). A critical feature of SPN is that SPN amplitude is greater at the right than at the left hemisphere. This feature suggests that the right hemisphere plays a significant role in the anticipation process. Some neuroimaging studies identified the anterior insula as a physiological source of SPN. The anterior insula is a part of the salience network that detects stimulus salience. Furthermore, recent neuroimaging studies reveal that the right anterior insula is involved in processing the salience outcome, whereas the left anterior insula is related to behavioral adaptation. The SPN study combining functional magnetic resonance imaging (fMRI) and ERP revealed that the right anterior insula showed increased activity preceding a stimulus, while the left anterior insula was not activated. Such studies lead to the hypothesis that saliency of an anticipated stimulus evokes the salience network in advance of a stimulus, and that this network then pre-activates other brain regions in perception of an anticipated stimulus. These processes can be shown as SPN variations in amplitude and cortical distribution. In general, SPN studies suggest that the saliency of an anticipated stimulus is a key factor in evoking anticipatory brain activity.

Keywords: stimulus-preceding negativity, insular cortex, salience network

Anticipation and event-related potentials (ERP)

Anticipation is a cognitive phenomenon characterized by an individual’s preparatory state of mind with respect to a forthcoming event or stimulus. Anticipation facilitates overt behavioral responses that render it possible for the individual to react faster to such events than without anticipation. On the other hand, anticipating an unwanted stressful event in the near future, for example, a student concerned about an upcoming examination, may sometimes also trigger strong anxiety. Investigating the neural mechanism of anticipation is also crucial for understanding how athletes exhibit fast and accurate movements in games, and why, on the other hand, some patients suffer from anticipatory anxiety in hospitals. In this review, we introduce studies concerned with stimulus-preceding negativity (SPN) that reflect anticipation. This entails a discussion of the neural mechanisms that underlie SPN and it leads to the revelation of a key factor in the evocation of brain activity related to anticipation.

Studies on human brain activity related to anticipation date from the 1960’s when the use of event-related potential (ERP) became popular1. The ERP is calculated from the electroencephalogram (EEG). To calculate ERP, an EEG is first determined by a duration with times fixed before and after recording a targeted event. This procedure is repeated over 30 times; then accumulated EEG records with identical durations are averaged. Thus, this averaging procedure eliminates EEG potentials unrelated to the event of interest, and those potentials related to the event are relatively enhanced. The enhanced potential is called an ERP. ERPs have been used to investigate many psychological and physiological phenomena. One of the merits of ERPs in investigations of human brain functions is their high temporal resolution. The ERP renders it possible to measure brain activity within scales of milliseconds; in turn, this high temporal resolution is crucial for investigating the anticipation activities of the human brain because anticipation is a time-related phenomenon.

Contingent negative variation (CNV) is a special type
of ERP that reflects anticipation\(^1\). CNV can be recorded using a warned reaction time paradigm, also known as an S1-S2 paradigm. A warned reaction paradigm begins with the presentation of a warning stimulus (S1), which is followed by a response stimulus (S2) within a few seconds. Participants are requested to make a motor response (e.g., a button press) as soon as possible after the S2. Since participants know the S2 will be presented with a fixed time interval from the S1, they can prepare their motor response, and this makes it possible to respond faster than when responding to S2 in the absence of S1. When we record the ERP using the S1-S2 paradigm, a slow negative potential shift can be observed between S1 and S2 (Fig. 1). This slow negative shift is labeled as the CNV\(^1\). Because the CNV can be recorded in the interval between S1 and S2, where participants anticipate the presentation of S2, the CNV is considered to be a manifestation of the anticipation process of the human brain.

Although CNV reflects an anticipation process, a noteworthy issue remains. In the S1-S2 interval, at least two brain activities are involved: one reflects motor preparation, whereas the other represents perceptual preparation. Because participants are requested to make a motor response at S2, there should be a preparatory process of the motor response. On the other hand, the process of preparation for stimulus perception (perceptual preparation) should also exist during the S1-S2 interval. Participants must also enlist preparatory attention to the S2, as well as preparing a motor response for S2. However, it is difficult to distinguish if observed CNV potential changes stem from perceptual activities or from modulations of muscular contraction power at S2 that affects the level of motor preparation.

Stimulus-preceding negativity (SPN)

In order to distinguish a perceptual-anticipation component from a motor-preparation component in CNV, a research group at Tilburg University in the Netherlands developed a time estimation task\(^2,3\). Their time estimation task consisted of a) an instruction stimulus, b) a cue stimulus, c) a motor response with time estimate, and d) a feedback stimulus. The instruction stimulus informed participants of a given time that an individual is required to estimate. That is, participants were told to press a button when they thought that the instructed time had elapsed. Such a task has the merit of temporally separating the perceptual anticipatory activity from motor preparation. Thus, motor preparation is conducted between the cue stimulus (b) and the motor response (c), and the perceptual anticipation can be elicited between the motor response (c) and the feedback stimulus (d). Using this task, they recorded two slow negative potentials (Fig. 2), one was observed before the motor response (between “b” and “c”), and the other preceded the feedback stimulus (between “c” and “d”). The slow negative potential before the motor response was the readiness potential (RP). The RP is a type of ERP that reflects motor preparation because the RP shows increased amplitude contralateral to the responding hand\(^4\). Another slow potential before the feedback stimulus was a previously unknown potential, which they labeled as the stimulus-preceding negativity (SPN). They discovered that the SPN amplitude at the right hemisphere was larger than recorded at the left hemisphere (right hemisphere preponderance) regardless of the responding hand (Fig. 2). This finding suggests that SPN is a non-motor potential. These discoveries have led

![Fig. 1] Waveforms of contingent negative variation (CNV). CNV is elicited between S1 and S2. C3: left central site of the scalp, C4: right central site of the scalp. Note that waveforms are depicted as negative up because negative amplitudes mean activation of the brain in the case of negative slow potentials like CNV.
to a general recognition of SPN as a neural manifestation of the anticipation process of the human brain.

**Functional significance of SPN: affective-motivational hypothesis**

After this discovery of SPN, these researchers pursued the questions about the type of stimuli that can evoke SPN. In their previous studies, they observed SPN happening prior to a feedback stimulus that conveyed information about task performance. However, it remained unclear if other kinds of stimuli could also elicit SPN. To address this question, they conducted an experiment using the time estimation task with two experimental conditions. One was a feedback condition, and the other was an instruction condition. In the feedback condition, a feedback stimulus conveyed accuracy information about their time estimates. In the instruction condition, an instruction stimulus conveyed information about the time that should be estimated in the next trial (6, 8 or 10 seconds). Specifically, the feedback conveyed information about the “past”, whereas the instruction stimulus conveyed information about the “future”. They compared SPNs before the feedback and the instruction stimuli. In the feedback condition, they successfully observed the SPN before the feedback stimulus. On the other hand, they failed to observe SPN in the instruction condition. This result suggests that merely conveying task relevant information is not a sufficient condition to evoke brain activity related to anticipation, and other factors could be involved in the occurrence of SPN.

This affective-motivational valence hypothesis was supported by a study reported by Böcker and his colleagues. In this study, a presented stimulus cue was followed by a mild electric shock with the probability of about 6%. They observed the SPN when participants anticipated the electric shock. This fear-induced SPN showed a fronto-central potential distribution that probably stemmed from the anterior cingulate cortex (ACC). In addition, Poli and colleagues recorded SPN occurring prior to presentations of affective pictures. They compared SPNs before high arousal affective pictures (e.g., involving erotic couples), and low arousal affective pictures (e.g., household objects). They found that the SPN before high arousal affective pictures was larger than the one before low arousal pictures. Furthermore, Ohgami et al. also found that adding monetary reward to the feedback stimulus increased SPN amplitudes. In addition, they discovered that the SPN amplitude in the left hemisphere was increased by monetary reward and, as a result, the right hemisphere preponderance of the SPN was diminished. Finally, it is also interesting that Mattox and colleagues found that mild Parkinson’s disease patients showed reduced SPN amplitudes especially in a high reward condition. The latter result implies that the dopaminergic system is related to SPN.

**Insular cortex as a physiological source of SPN**

The studies described above suggested that SPN may be related to affective-motivational valence. However, at that time physiological sources of SPN had not been clarified. Regarding the physiological sources of SPN, Böcker and colleagues conducted a dipole source analysis on...
SPN. The dipole source analysis is a method designed to detect sources of ERP by solving a mathematical inverse problem. Using this method, they assumed that the insular cortex is one source of SPN. Taking into account previous SPN studies and the results of their dipole source analysis, they concluded that the insular cortex may be involved in an anticipatory attention process; moreover, it was also suspected that the affective-motivational valence functions as a key factor in eliciting SPN. These findings are intriguing. This is because, at the time, the insular cortex was seen as the gustatory area, or the brain region related to pain. However, these findings broaden the interpretation, suggesting that the insular cortex is involved in affective motivational processing. Later functional magnetic resonance imaging (fMRI) studies have supported their suggestion\(^{13}\).

In addition to the dipole study, Brunia and colleagues\(^{12}\) conducted a positron emission tomography (PET) study using the time estimation task. They aimed to ascertain if the insula contributes to the occurrence of SPN. In this study, they compared brain activation in true feedback and false feedback conditions, and confirmed the activation in the insular cortex, especially in the right hemisphere. We have also replicated their PET study using a block-design fMRI\(^{13}\). By subtracting brain activation in the false feedback condition from brain activation in the true feedback condition, we confirmed activation in the right insula, as well as activation in the middle frontal gyrus, thalamus, and striatum\(^{13}\). In addition to the block-design fMRI, we also employed an event-related design fMRI using the time estimation task. An event-related design fMRI has better temporal resolution than the block-design fMRI. Although the activation in the insular cortex was found in the block-design fMRI, it was unclear precisely ‘when’ the insular cortex was activated during this task because the block-design fMRI has lower temporal resolution. Using the event-related design fMRI, we confirmed that the insular cortex was indeed activated when participants were anticipating the feedback stimulus\(^{14}\). In particular, we found that the anterior part of the insular cortex (anterior insula) was activated during anticipation. Furthermore, the right anterior insula increased in activity as the time estimation task increased in difficulty. These studies using dipole, PET, and fMRI support the notion that the insular cortex is one of the physiological sources of SPN.

**Insular cortex is a key region of salience network**

The human insular cortex is located at the bottom of the Sylvian fissure. As its name indicates, the insular cortex looks like an island (Fig. 3). Anatomically, the insular cortex can be divided into three sub-regions: the anterior insula, middle insula, and posterior insula\(^{15}\). The posterior insula is involved in somatomotor processing\(^{16}\), and the anterior insula integrates autonomic and interoceptive information\(^{17,18}\). The insular cortex has strong anatomical and functional connections to the ACC\(^{19}\).

It is well known that the insular cortex plays a key role in the salience network of the human brain\(^{20}\). In our daily life, we receive so much endogenous and exogenous information from our bodies and environment. The salience network identifies the most important information among these stimuli. The salience network contributes to a variety of complex brain functions, including communication, social behavior, and self-awareness through the integration of sensory, emotional, and cognitive information\(^{17}\). Because the salience network also engages anticipation tasks\(^{21}\), it is plausible to hypothesize that the salience network contributes to the occurrence of SPN. Regarding the function of the anterior insula as the salience network, Gu and colleagues\(^{19}\) proposed that the anterior insula is involved in interoceptive predictions. According to this proposal, the anterior insula sends interoceptive predictions to the autonomic system. Then, the anterior insula receives a prediction error from the autonomic system. If this concept is correct, then the anterior insula should be activated before the event that evokes interoceptive responses in order to send interoceptive predictions. Since SPN occurs before a stimulus and its physiological source is the anterior insula, it is possible that the anterior insula becomes active before the occurrence of a stimulus that evokes interoceptive responses.

In order to determine whether the anterior insula is activated before the stimulus, we performed an fMRI-constrained source analysis combining fMRI and ERP results to precisely identify the location and timing of activation\(^{22}\). We employed the time estimation task conventionally used in SPN studies, and analyzed the brain activations in the pre-feedback anticipation phase where the subjects were anticipating feedback stimulus. In this fMRI-constrained source analysis, dipole locations

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**Fig. 3** Anatomical model of the insular cortex. The human insular cortex located at the bottom of the Sylvian fissure. The insular cortex can be divided into the anterior insula, middle insula, and posterior insula.
were identified by the fMRI results. As expected, fMRI results successfully indicated activations in the bilateral anterior insula (Fig. 4). We also found activation in the ACC, which is a node of the salience network. Based on these fMRI results, we seeded dipoles at activated brain regions, and source wave activities for each dipole were estimated using the ERP data. With this process, the temporal activities of the identified brain regions can be depicted on a scale of milliseconds. Fig. 4 shows temporal activities in the left and right anterior insula and ACC. The onset amplitude of the right anterior insula was significantly different from zero. On the other hand, the onset amplitude of the left anterior insula was not significantly different from zero. These results suggest that the right anterior insula was activated about 2800 ms before the feedback stimulus, whereas the left anterior insula was not activated before the stimulus. The ACC, which is involved in the salient network, also started its activation about 2600 ms before the feedback stimulus (Fig. 4). Co-activation of ACC and the right anterior insula also supports the notion that the salience network contributes to this anticipation process.

Right hemisphere preponderance of SPN and functional difference between the left and right anterior insula

Results of the fMRI-constrained source analysis revealed that the right anterior insula was activated before the feedback stimulus, while the left anterior insula was not activated. As mentioned above, the SPN also shows a right hemisphere preponderance. These features lead to the possibility that the right anterior insula may support a different function in the anticipation process when compared to that of the left anterior insula. Regarding the functional difference between the left and the right anterior insula, Spätí and colleagues conducted an fMRI experiment using a dynamically adapted motion prediction task. In this task, two balls move at different speeds, from respectively different starting points, toward a finish line. The task was to predict which ball would cross the finish line first. Two conditions were a self-attributed condition and an external-attributed condition. In the self-attributed condition...

Fig. 4 Temporal activities in the bilateral anterior insula and anterior cingulate cortex (ACC). Locations of the anterior insula and ACC were identified by fMRI results (left side). 3D topographical maps on the right side show an estimated potential distribution that the brain region produced. Black triangles indicate the time that amplitude reached 30% of the maximum amplitude before the feedback stimulus. The right anterior insula started its activation 2805 ms before the feedback stimulus. The source wave amplitude at this onset was significantly different from zero. The onset amplitude of the left anterior insula was not significantly different from zero. The ACC started its activation about 2625 ms before the feedback stimulus. The dipole at the ACC produced a positive potential distribution at the scalp level. M: onset of button press, FB: onset of the feedback stimulus (adapted from Kotani et al., 2015).
condition, monetary gain or loss depended on the prediction made by participants. In the external-attributed condition, gain or loss depended on a prediction of a personal computer (PC). The results indicated that the left anterior insula showed greater activity in the self-attributed than in the external-attributed condition on both loss and gain trials. This means that the left anterior insula is involved in a behavioral control process that optimizes subsequent behaviors in maximizing monetary gain. On the other hand, the right anterior insula showed greater activity in the self-attributed condition only in loss trials. The authors interpreted this to mean that the right anterior insula is mainly involved in processing the salience of an outcome because a loss would be more salient for participants than a gain. Ohgami et al. (2006) showed that there was no hemisphere difference of the SPN amplitude in a monetary reward (gain) condition. On the other hand, the monetary punishment (loss) showed right hemisphere preponderance. These results coincide with the idea that the left SPN is related to behavioral adaptations while the right SPN is involved in salience processing based on interoceptive prediction.

Switching function of the salience network and variation of SPN

The role of the salience network includes controlling other brain networks. The salience network switches the default mode network to the central-executive network, and vice versa, based on detection of saliency as well as cognitive demands. The default mode network is the network that is activated during a task-free resting state, that is, “OFF state”. Alternatively, the central-executive network is the one that is activated during a task-active situation, that is, “ON state”. This means that the salience network has an ON-OFF switching function to produce an optimal cognitive state. In addition to the ON-OFF switching function, the right anterior insula has a function that modulates and activates other brain regions based on the modality of stimulus conveying salient information.

Regarding stimulus modality, the SPN amplitude can also vary with stimulus modality of the anticipated stimulus. For example, when participants anticipate an auditory stimulus that conveys salient information, the SPN amplitude at the fronto-temporal area is increased. On the other hand, if participants anticipate a visual stimulus, the SPN amplitude at the occipital area is increased. The scalp potential distribution of the SPN also varies according to the stimulus modality. As mentioned above, the right anterior insula activates other brain regions, and this region is a source of the SPN. The salience network, including the right anterior insula, can pre-activate other brain regions based on stimulus modality and cognitive demands of the salient event. In turn, such pre-activations may be reflected in amplitudes and scalp distributions of SPN. In addition to varying amplitudes and scalp potentials, the salience network might also control the timing of activation in a brain region according to stimulus content. For example, anticipation of verbal and symbolic stimuli increases the amplitude of the late component of SPN, which shows the maximum amplitude during the latter part of the anticipating interval. On the other hand, anticipation of facial stimuli increases the amplitude of the early component of SPN that shows the maximum amplitude during the earlier part of an anticipatory interval. This means that face anticipation is faster than verbal and symbolic stimuli. This is probably due to the fact that the level of cognitive demands of facial stimuli differs from that of other stimuli, and also because the timing of pre-activation in face-related regions is advanced by the salience network.

Switching function of the salience network and variation of SPN

Regarding cognitive demands, the SPN amplitude before a feedback stimulus is also affected by the level of task learning. That is, it has been shown that SPN amplitude decreases as learning progresses. This may be due to the reduced saliency of the feedback stimulus because cognitive demands diminish as learning progresses. Furthermore, the SPN amplitude is also affected by self-involvement, specifically the level of an individual’s participation with a task. If a computer-determined decision is made on a bet in a gambling task (low self-involvement), SPN amplitudes before a feedback stimulus about the result drop. On the other hand, if a participant made a decision on the bet (high self-involvement), SPN amplitudes preceding the feedback stimulus appear to increase. Since cognitive demands increase as self-involvement increases, SPN amplitudes will also increase when participants make their decisions.

As mentioned above, the salience network detects saliency of stimuli and events. In addition, this network modulates other brain regions based on cognitive demands and the modality of stimulus. This may explain why stimulus modality, level of learning and self-involvement all lead to variations in amplitude, cortical distribution, and timing of activation of SPN.

Summary

Conventionally, the functional significance of SPN was discussed in terms of affective-motivational valence of the anticipated stimulus. More recent studies expand this view to include the idea that saliency of an anticipated stimulus evokes the salience network before a stimulus onset, and that the salience network pre-activates other brain regions involved in perception of the anticipated stimulus. This hypothesis suggests that saliency of the anticipated event is a key factor in evoking brain activity related to anticipation.

Menon proposed the idea that dysfunction of the salience network either causes aberrant activity in the central executive network and/or in the default mode network leading to major psychopathological symptoms.
The involvement of the salience network in the anticipation process may explain why some patients suffer from anticipatory anxiety. If Menon’s idea is correct, then SPN can be employed as an index of abnormalities of the salient network that cause psychiatric disorders. Indeed, some studies have investigated the role of SPN in social anxiety\(^3\), autism spectrum disorders of children\(^4\), Parkinson’s disease\(^5\), and schizophrenia\(^6\). As Menon\(^7\) noted, the salience network is a key brain system for integrating cognition, action, and feelings. In addition, a part of the salience network is a physiological source of SPN. Since SPN has a high temporal resolution, it may be a useful index for describing dynamic temporal activity of the salience network, one that can reveal how a salience network modulates other brain regions.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this article.

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