Distinctive types of aversiveness are represented as the same in a portion of the dorsal anterior cingulate cortex: An fMRI study with the cue paradigm

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Abstract—Some studies have argued that the dorsal anterior cingulate cortex (dACC) is generally activated in response to aversive information, including pain, negative affect, and cognitive conflict. Other studies have claimed that the dACC has subdivisions, and each division has a specific function. By manipulating emotionally and cognitively aversive cues, the present study determined whether the dACC is generally responsive to aversiveness or it has subdivisions for specific forms of aversiveness. Conjunction functional magnetic resonance imaging (fMRI) analysis showed that emotionally and cognitively aversive cues activated the same portion of the dACC. When these cues were contiguously presented, the region demonstrated additive activity, further supporting the overlapping representation of the two different forms of aversiveness in the dACC. Additional effective connectivity analysis showed that the dACC was co-activated with different brain regions depending on the cue type, characterizing its behavioral control mechanism. Complementary multivariate analyses showed that the reaction time was negatively correlated with the activity of the dACC and that the activity of the dACC under the emotional cue was predicted by the individual state anxiety score but not under the cognitive cue. We also found that the superior part of the dACC was uniquely activated in response to cognitively aversive cues, partially supporting the functional segregation account. Collectively, our results provide evidence that the specific locus of the dACC is generally responsive to distinctive motivational information, whereas the other loci may have segregated functions. Discussion includes recent neurocomputational theories that seem to satisfactorily account for the present results. © 2022 The Author(s). Published by Elsevier Ltd on behalf of IBRO. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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INTRODUCTION

The anterior part of the middle cingulate cortex, often referred to as the dorsal anterior cingulate cortex (dACC), has been reported to be involved in various psychological functions, including rewards, errors, inexperienced outcomes, surprise, conflict, decision costs, uncertainty, learning, and arousal (Ebitz and Hayden, 2016). To specify the fundamental function of the dACC, several studies have proposed influential theories for its neuro-computational mechanism: foraging theories, control theories, predicted outcome-response theories, and reinforcement-learning theories (Alexander and Brown, 2011; Silvetti et al., 2014; Kolling et al., 2016; Shenhav et al., 2016; Silvestrini et al., 2022). Other studies have investigated the unitary or sub-dimensional properties of the dACC. For instance, using the activation likelihood estimate, Shackman et al. (Shackman et al., 2011) suggested that the dACC is commonly activated in response to negative affect, pain, and cognitive control. With this finding, the authors argued that the dACC plays a primary role in adaptive control by facilitating a change in an ongoing behavior to a more adaptive one, which is motivated by a general aversive environment such as conflict or pain. Subsequent studies have also shown the domain-general nature of the medial frontal cortex, which includes the dACC (de la Vega et al., 2016; Braem et al., 2017; Vermeylen et al., 2020). For instance, Braem et al. (Braem et al., 2017) found common activity of the dACC in cognitive conflict and negative affect and suggested that the dACC processed the aversive aspect of cognitive conflict. Using multivariate pattern analyses, Vermeylen et al. (Vermeylen et al., 2020) provided evidence that the medial frontal cortex, including the dACC, successfully classified both conflict and affect, further
supporting the idea that the dACC extracts the aversive nature of psychological challenges.

However, it has been suggested that dACC can be segregated by designated functions (e.g., Bush et al., 2000). Jahn et al. (Jahn et al., 2016) incorporated prediction, pain, and cognitive conflict into a single task and found that each function activated distinct regions of the medial prefrontal cortex, including the dACC. Using a large-scale meta-analysis, de la Vega et al. (de la Vega et al., 2016) identified three core regions of the medial frontal cortex where the middle zone corresponding to the dACC commonly responded to cognitive control, negative affect, pain, and decision-making. Although this finding is consistent with aversive-driven behavioral adjustment by action-outcome uncertainty (Shackman et al., 2011), further analysis showed that the dorsal portion is more connected to the cognitive control region and the ventral portion to the subcortical regions. These findings seem to agree with the divisional account of the dACC. A subsequent study with representational similarity analysis also provided evidence for the divisional account (Kragel et al., 2018).

In the present study, we employed two different types of aversive cues to reconcile discrepancies between the studies. In previous studies, different types of tasks were administered, and each task-specific effect might be reflected by the activity in distinctive loci of the medial prefrontal cortex. Introducing aversive cues is a potential means of removing such task-specific effects. This discrepancy may also be resolved by continguously presenting two different aversive cues and examining the consequent dACC activity. If the contiguous presentation of those cues produces additive activity of the dACC relative to single aversive cues, it may allow us to argue that the dACC regards different types of aversiveness as the same. Given that the dACC can integrate various aversive stimuli (Shackman et al., 2011), our prediction of the additive responsiveness of the dACC is reasonable.

To investigate the function of the dACC, we introduced cognitively or emotionally aversive cue stimuli as stated above. This manipulation is preferable to minimize task-specific confounding effects. The cue paradigm has been repeatedly employed in previous studies to compare distinctive cognitive processes by minimizing the effects of actual task execution (Krebs et al., 2012; Vassena et al., 2014). For instance, Krebs et al. (Krebs et al., 2012) used a cueing paradigm that distinguished neural responses reflecting anticipated reward and anticipated task difficulty level and found that the two processes were commonly represented by several neural regions, including the dopaminergic midbrain regions and cortico-striatal regions. Applying the cueing paradigm to the present study, we introduced cognitive cues as an indication of a difficult task that demanded higher cognitive effort; a quick response to a subsequent target surrounded by distractors was required. The emotional cue was associated with fear of pain; the pain cue involved the delivery of an aversive electric shock when a participant had an incorrect response. These cues are selected based on the finding that cognitive effort and pain induce similar muscle contractions on the upper face (see Shackman et al., 2011). If each cue activated the same loci of the dACC, this would support the hypothesis that the dACC is responsive to aversive content in general. Furthermore, if the dACC shows summated activity when difficulty and pain cues are continguously presented, this would further support the unitary account that two different types of aversive information are overlappingly represented by the dACC. In addition to dACC activity, cue manipulation was predicted to affect behavioral and physiological responses. Participants were expected to show a quick behavioral response according to an increase in cue aversion, which demands greater cognitive control as signaled by the dACC. We also measured electrodermal activity (EDA) while participants observed the cue stimuli to determine whether both cues produced higher arousal, potentially associated with aversive responses.

Furthermore, the present investigation has some implications for neurocomputational studies of the dACC. As stated above, the dACC is proposed to play a significant role in computing to optimize neurobiological problems for adaptive behaviors. A recent review bridges the traditional motivation intensity theory on goal-oriented behaviors with the neurocomputational theories of the dACC to specify the neural mechanism underlying the adaptive allocation of control (Silvestrini et al., 2022). Two influential models are comprehensively depicted in the literature: the expected value control (EVC) and reinforcement meta-learner (RML) models. In the EVC model, the dACC computes the control signal by summating the expected values of available outcomes and subtracting costs associated with the control implementation (Shenhav et al., 2013). In the RML model (Silvetti et al., 2014), the dACC plays the Critic role and computes reward expectations given a specific state of the environment and subsequent occurrence of a reward. The computational process of the dACC allows us to adjust our behavior in a volatile environment. The updated RML model (Silvetti et al., 2018) includes brainstem neurotransmitter systems (i.e., dopamine and norepinephrine) to be more biologically plausible. If our results favor the unified account in which some loci of the dACC are responsive to distinctive aversiveness, it may mean that the dACC has a general computational mechanism; namely, the dACC calculates variables including the value of reward expectation (i.e., correct response) given by aversive cues and associated effort. However, if our results favor a distinctive account, we may need to explore distinctive neurocomputational algorithms for each subdivision area.

The neural activity of the dACC was measured during the presentation of the stimuli using fMRI. Conjunction analysis was used to investigate the hypothesis that cognitively and emotionally aversive information are commonly processed in the dACC. The activity of the dACC was further analyzed to determine whether the combination of the two aversive information sources produced an additive activation of the dACC. Additionally, effective connectivity analysis was used to identify how the dACC was coupled with other regions depending on the type of cue. If the dACC is involved in
the adaptive control of behavior, it is predicted that it exerts its effect on appropriate brain regions depending on the task demand.

**EXPERIMENTAL PROCEDURES**

Participants
Twenty-eight graduate and undergraduate students participated in this study ($M = 22.03$, $SD = 4.75$, 14 females). All participants were healthy volunteers with normal or corrected-to-normal vision. Before the experiment, the experimenter provided a detailed description of the study and obtained informed consent from the participants. The study protocol was approved by the ethics committee of the National Institute of Information and Communications Technology. Participants received monetary rewards (5,000 yen, including transportation expenses) for their participation.

Stimulus
Twenty facial photographs with emotional expressions were used (Ekman and Friesen, 1976). Half of them were smiling, and the other half were fearful. These face stimuli were employed in the Stroop-Flanker task. Three faces were arranged horizontally, and an emotional word (“happy” or “fear”) was superimposed in the middle of the face. During the fMRI session, the stimuli were projected onto a screen using a mirror mounted on a head radiofrequency coil.

Two fractal images were used as conditioned stimuli to develop fear conditioning. For a given participant, one image was associated with an electrical shock, whereas the other was not paired with anything. An electrical shock lasting 1,000 ms was produced and delivered using STMSOC (BIOPAC Systems Inc., Goleta, CA, USA).

Procedure
After completing the consent form, participants performed the Stroop-Flanker task. Thirty-two trials were permitted, and participants were encouraged to perform the task as accurately and quickly as possible. During the task, three faces were presented horizontally, and a word (“happy” or “fear”) was superimposed on the middle face. The participants were required to judge the emotional identity (happy or fearful) of the middle face within 2 s. Two conditions were presented, congruent and incongruent. For the congruent condition, the emotional identity of the middle face was congruent with that of the adjacent faces, as well as that of the word. In the incongruent condition, the emotional identity of the middle face was incongruent with that of the neighboring faces and the superimposed word. The task aimed to calibrate the individual reaction time to adjust the task difficulty for the following sessions.

As stated in the Introduction, the present study used a cueing paradigm to specify the function of the dACC. In various theories on the dACC (Silvetti et al., 2014; Shenhav et al., 2016; Silvestrini et al., 2022), the region is proposed to be responsive to effortful tasks. Because we used a cueing paradigm, we needed to associate cues with an effortful task; otherwise, the dACC was unlikely to be activated in response to the cues. Therefore, we included two distractors (i.e., words and two faces) in the incongruent condition. We also included emotional distractors that captured attention (Whalen et al., 2006). As participants were unable to predict the congruency of the trial at the cue phase, they were required to prepare for the effortful condition (i.e., the incongruent condition), which was expected to recruit the dACC.

After calibration, we organized a fear conditioning session in which a fractal image was paired with an electrical shock. Two electrodes were attached to the left forearm of each participant. Before starting conditioning, we individually adjusted the intensity of the electrical shock. Using an equipment dial, we gradually increased the intensity until participants reported that they could no longer tolerate it. Defining this as the threshold, we slightly decreased the intensity and used it for fear conditioning. For the fear block, a single electric shock was delivered 1,000 ms after the fractal image, which was repeated five times. For the neutral block, no shock was delivered five times per row. The fear and neutral blocks were alternately repeated four times. Thus, 20 electric shocks were delivered.

Before scanning, we introduced the main experimental task (Fig. 1), and the participants performed 32 practice trials. The task was mostly identical to the calibration task except for the inclusion of cues. Two cues were presented sequentially before the Stroop-Flanker task. The first cue indicated a time window for accepting the participant's responses. Two time windows (short and long) were used. For the short window, a quick response was required from participants; otherwise, the response was considered incorrect. The time window was individually adjusted based on the performance of the calibration task. The reaction time in the top 25% of the total distribution during the calibration was used as an individual short time window, which was shown as a text message (e.g., 500 ms). The long time window was always two seconds, which was displayed as another text message (2 s). The first cue was presented for 1 s. After a 500 ms inter-cue-interval, the second cue was presented for 1 s. The cue indicated the presence or absence of an electric shock when participants responded incorrectly. Fractal images presented during fear conditioning were used as cues. Therefore, a combination of two cues resulted in four possible conditions: Shock-Short, Shock-Long, No Shock-Short, and No Shock-Long. The inter-stimulus interval (ISI) between the second cue and the target stimulus (i.e., faces and a word) was randomly jittered (2,800–4,200 ms). Feedback on their responses was provided after another jittered ISI (2,800–4,200 ms) following a target stimulus. Immediately after the incorrect response, an electrical shock was delivered under the shock conditions. Under the no shock conditions, only text messages (i.e., “correct” or “incorrect”) were presented at the end of a trial. The inter-trial intervals were also jittered, ranging from 4,200 to 8,400 ms.
Table 1 summarizes terms used in the experimental task, which may help readers comprehend the task procedure.

At the end of the experiment, we measured participants’ distress levels during the Stroop-Flanker task using the state-trait anxiety inventory (Spielberger, 1989). We specifically used 20 items to measure state anxiety and asked the participants to rate each item while remembering their emotional state during the task. Individual distress levels were scored according to the manual (Spielberger, 1989).

In the MRI scanner, participants held a response pad with two buttons, and they were instructed to press the left button for a happy face and the right button for fear. We ran two fMRI sessions, and 64 trials were performed during each session, which resulted in 32 trials in each “cue” condition (i.e., Shock-Short, Shock-Long, No Shock-Short, and No Shock-Long). Eight experimental blocks were prepared, each containing 16 different trial types (four cues × two congruencies × two emotions). In each block, trial types were randomly ordered for each participant. Stimulus presentation and response retrieval were regulated using commercial software (Presentation, Neurobehavioral Systems, Inc., Albany, CA, USA). The EDA was also measured using EDA 100C MRI (BIOPAC Systems Inc., Goleta, CA). The electrodes were attached to the index and middle fingers of the participant’s left hand, and EDA was recorded at a sampling rate of 2,000 Hz throughout the scanning.

fMRI data acquisition

Functional images were obtained using a 3.0-T MRI scanner (MAGNETON Prisma (3 T); Siemens, Munich, Germany). Head motion was minimized with a forehead strap and comfortable padding around the participant’s head. Functional images (1,022 scans/session) that were sensitive to blood oxygen level-dependent contrasts were acquired using a multiband sequence (TR = 1,400 ms, TE = 30 ms, flip angle = 70°, 64 × 64 at 3 mm in-plane resolution, 3-mm thickness, 51 contiguous oblique axial slices parallel to the AC–PC line). Field map images were acquired before each fMRI scan (TR = 753 ms, TE 1 = 5.16 ms, TE
Table 1. Descriptions of terms associated with experimental tasks.

| Term          | Description                                                                                                                                 |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Stroop-Franker Task | Three face images with an emotional expression (happy or fear) were presented horizontally, and one emotional word (happy or fear) was superimposed on the middle face. |
| Congruent Trial | The middle target face was always congruent with the neighboring faces and emotional words superimposed on the middle face in the Stroop-Franker task. |
| Incongruent Trial | The middle target face was always incongruent with the neighboring faces and emotional words superimposed on the middle face in the Stroop-Franker task. |
| Calibration Task | The task measured reaction time of a given participant in Stroop-Franker Task.                                                                 |
| Fear Conditioning | An electric shock was associated with a fractal image to induce an emotionally aversive state.                                                |
| Main Task      | Two cues were presented contiguously prior to a Stroop-Franker stimulus. Time cue (short or long) was presented first for 1000 ms, followed by a pain cue (pain or no pain) with 500 ms ISI. |
| Short Time Cue  | Notify participants that the response time limit is short (Cognitively aversive).                                                             |
| Long Time Cue   | The limit was individually calibrated, and presented as a unit of ms.                                                                     |
| Pain Cue        | Notify participants that an electric shock will be given when making an incorrect response or their response time exceeds the time limit (Emotionally Aversive). |
| No Pain Cue     | Notify participants that an electric shock will not be given when making an incorrect response or their response time exceeds the time limit (Emotionally not Aversive). |

2 = 7.62 ms, flip angle = 90°, 64 × 64 at 3 mm in-plane resolution, 3-mm thickness, 51 contiguous oblique axial slices parallel to the AC–PC line. After the experimental scans, anatomical images were collected for all participants (TR = 1,900 ms, TE = 3.37 ms, flip angle = 9°; voxel size = 1 × 1 × 1 mm).

fMRI data analysis

The imaging data were analyzed using SPM12 (Wellcome Trust Center for Imaging, London, UK) running on MATLAB 8.30 (Mathworks Inc., Sherbon, MA). The slice timing correction was performed using the middle slice as a reference. Head motion was corrected for the first functional image. A voxel displacement image was obtained using the field map image and applied to the EPI images to avoid distortion. The EPI images were then co-registered to individual T1 anatomical images that had been segmented. The co-registered images were normalized to a common brain space (the MNI template provided by SPM12), where the individual voxel sizes were 2 × 2 × 2. Subsequently, the images were smoothed using a Gaussian filter (full-width half-maximum) of 6 mm.

To model the functional images, we used a high-pass filter (1/128 Hz) to eliminate baseline drifts and an autoregression model (1) to correct the temporally correlated data. Fourteen regressors were convolved with the canonical hemodynamic response function. Four regressors corresponded to the cue phases (two pain conditions × two time conditions) with a duration of 2.8 s to capture the trial-subcomponent brain activity (Zarahn et al., 1997) during successive cue presentation (2.5 s). Another eight regressors corresponded to the stimulus phases (two pain conditions × two time conditions × two congruency conditions), with a duration of 0 s. The remaining two regressors were for feedback conditions (correct vs incorrect), with a duration of 2.8 s. Only the correct trials were included as regressors during the cue and stimulus phases. Six motion regressors were included in the model. Because we were primarily interested in neural activity during the cue phases, four main contrasts were created for each individual: Pain-Short, Pain-Long, No Pain-Short, and No Pain-Long. For group analysis, a full-factorial design was used to specify the brain regions, with two experimental factors (pain and time).

Because the present study focused on the dACC, we created an ROI image of the dACC using AAL structural ROIs (Tzourio-Mazoyer et al., 2002). First, we combined the midcingulate regions (i.e., the bilateral MNI_Cingulum_Mid) and the anterior cingulate regions (i.e., the bilateral MNI_Cingulum_Ant) using Marsbar software (Tzourio-Mazoyer et al., 2002). Next, we created a sphere cluster image with a radius of 20 mm, and its center coordinates were x = −1, y = 10, and z = 46 in MNI coor-
coordinates, as reported in a previous study (Shackman et al., 2011) where they were reported in Talairach coordinates (0, 12, 42). Finally, we overlapped the structural and spherical ROI images and used the overlapped region as the dACC ROI (Fig. 2). The image was used in the small-volume correction analysis with a statistical threshold of $p < .05$ (familywise error rate (FWE) corrected for multiple comparisons) at both the cluster and voxel levels.

To investigate whether the dACC was commonly activated in response to cognitively and emotionally aversive cues, we performed a conjunction analysis using SPM12. Small volume correction analysis was performed with a statistical threshold of $p < .05$ (FWE corrected for multiple comparisons) at both the cluster and voxel levels. A small-volume correction analysis was performed for the dACC. To identify brain regions uniquely activated in response to emotionally or cognitively aversive cues, an exclusive mask contrast (e.g., a main effect of time) was applied to the main contrast (e.g., a main effect of pain). For the analyses, we used a statistical threshold of $p < .001$ (uncorrected for multiple comparisons) at the voxel level and $p < .05$ (FWE corrected for multiple comparisons) at the cluster level.

Effective connectivity analysis

To measure effective connectivity from the dACC, we performed a psycho-physiological interaction (PPI) analysis using SPM12, as it is recommended for factorial designs (Friston et al., 1997). Individual volume of interest (VOI) was determined using an individual fixed model. Specifically, we located the center of the VOIs by searching for the voxel near the coordinate $x = 12$, $y = 16$, and $z = 36$, which was the overlapped dACC region commonly activated under the pain and short-time window conditions in the group analysis. A sphere with an 8-mm VOI surrounding the central coordinate was created, and the cluster was defined as the individual seed region for PPI analysis. We referred to the overlapped region to locate individual VOI because the SPM software allowed us to select activated voxels as their central coordinates. Therefore, it should be noted that our VOI selection was biased by the general linear model (GLM) conjunction results and that the obtained PPI results can only be applied in the present experimental context. By extracting the BOLD signal from the seed region, two interaction terms were formed. One was the term between the source signal and the main effect of pain [Pain (Pain_Short + Pain_Long) > No Pain (No Pain_Short + No Pain_Long)]. The second was the term between the source signal and the main effect of time [Short (Pain_Short + No Pain_Short) > Long (Pain_Long + No Pain_Long)]. A GLM was created, including regressors for the interaction between the dACC and the main effect of the pain, the original dACC eigen-variate, and a vector of the pain condition. Similarly, another GLM was created to determine the main effect of time. In each model, a contrast image of the interaction term was generated for each participant. The one-sample $t$-test was used for a random-effects analysis to identify the regions coupled with the dACC for the pain condition. The same analysis was performed for the time condition. Statistical thresholds of $p < .001$ (uncorrected for multiple comparisons) at the voxel level and $p < .05$ (FWE corrected for multiple comparisons) at the cluster level were used.

Electrodermal activity (EDA) analysis

The EDA was preprocessed with Acknowledge software 4.2.0 (BIOPAC Systems, Inc., Goleta, CA, USA). To construct the phasic EDA, we applied a 0.05 Hz high-pass filter. The obtained EDA was resampled for 200 ms by averaging the 400 data points. Time-series data were statistically analyzed using R software (R Foundation for Statistical Computing, Vienna, Austria).

Experimental design and statistical analysis

To assess behavioral performance during the Stroop Flanker task, we used a 2 (pain) $\times$ 2 (time) $\times$ 20 (time points) factorial design. A repeated-measures ANOVA was used with an alpha level of $p < .05$ as the statistical threshold. Shaffer’s modified sequentially rejective Bonferroni procedure was used for post-hoc testing. Statistical analysis was performed using the R software.

A 2 (pain) $\times$ 2 (time) $\times$ 20 (time points) factorial design was used for EDA analysis. Because the present study focused on EDA in response to cognitively and emotionally aversive cues, a 4-s EDA after cue presentation was reported. The statistical threshold and multiple comparison methods were identical for the behavioral data.

As described above, univariate fMRI analysis was performed using a factorial design built into the SPM12. A one-sample $t$-test was used for PPI analyses.

Fig. 2. Anatomical ROI of the dorsal anterior cingulate cortex.
RESULTS

Behavioral results

The mean reaction time in the Stroop-Flanker task is shown in Fig. 3 and Table 2. The reaction time for the pain conditions was shorter than that for the no-pain condition when the factors of time and congruency collapsed (Fig. 3, left). The reaction time was shorter for the short-time window conditions than for the long-time window conditions when the factors of pain and congruency collapsed (Fig. 3, right). Similarly, the reaction time was shorter for the congruent condition than for the incongruent condition when the factors of pain and time collapsed. Three-way repeated measures ANOVA showed a main effect of pain ($F(1, 27) = 18.31, p < .001$), response time window ($F(1, 27) = 12.37, p = .002$), and congruency ($F(1, 27) = 149.46, p < .001$). The two-way interaction between pain and response time window showed a trend toward significance ($F(1, 27) = 3.83, p = .06$). Similarly, the two-way interaction between pain and congruency showed a trend toward significance ($F(1, 27) = 3.24, p = .08$). The two-way interaction between the time window and congruency was not statistically significant ($F(1, 27) = 0.24, p = .62$), and the three-way interaction was also not statistically significant ($F(1, 27) = 1.13, p = .30$).

The mean accuracy for the Stroop-Flanker task is presented in Fig. 4 and Table 3. Accuracy was lower for the short than for the long time window conditions when the factors of pain and congruency collapsed. Accuracy was higher for the congruent condition than for the incongruent condition when the factors of pain and time collapsed. A three-way repeated-measures ANOVA showed a main effect of time ($F(1, 27) = 6.00, p = .02$) and congruency ($F(1, 27) = 6.00, p = .02$). The main effect of pain was not statistically significant ($F(1, 27) = 0.70, p = .41$). Neither of the two-way interactions was significant: pain × time ($F(1, 27) = 2.70, p = .11$), pain × congruency ($F(1, 27) = 0.20, p = .65$), and time × congruency ($F(1, 27) = 2.86, p = .10$). The three-way interaction was not statistically significant ($F(1, 27) < 0.01, p = .93$).

Electrodermal activity result

The EDA time-course amplitudes in response to the pain and time cues are shown in Fig. 5. The time-course EDA amplitude was modulated by pain and time cues. For the initial 1,200 ms, after the time cue was presented, the amplitudes of the pain and no-pain conditions did not differ. However, at 1,400 ms, when the pain cue was about to be presented, the EDA amplitude increased for the pain condition, which continued for the rest of the period. However, the EDA amplitude of the short conditions was greater than that of the long conditions, 400 ms after the presentation of the time cue, and this difference was maintained for the rest of the period. A three-way ANOVA showed significant main effects of pain ($F(1, 27) = 9.94, p < .001$) and the time window ($F(1, 27) = 10.31, p < .001$). Significant two-way interactions were also found between the factors of pain and time point ($F[19, 513] = 6.33, p < .001$) as well as the time window and time point ($F[19, 513] = 2.51, p < .001$). Shaffer’s modified sequentially rejective Bonferroni procedure, applied to the pain × time point interaction, showed that the EDA amplitude for the initial 1,200 ms did not differ between the pain and no-pain conditions ($p > .05$). However, the EDA of the pain condition was greater than that of the no-pain condition.
from 1,400 to 4,000 ms (all $p$s < 0.05). The post-hoc analysis applied to the time window x time point interaction showed that the EDA amplitude of the short conditions was greater than that of the long conditions for 4,000 ms, except for the initial 200 ms ($p = .06$). The main effect of the time point was not statistically significant ($F_{[19, 513]} = 1.53, p = .07$). Neither the two-way interaction between the factors of pain and the time window ($F_{[1, 27]} = 0.10, p = .75$) nor the three-way interaction ($F_{[19, 513]} = 0.66, p = .86$) were statistically significant.

### fMRI result

A conjunction analysis of the main effects of pain and time showed common activation of the dACC (Fig. 6, top); the peak coordinates were $x = 14$, $y = 14$, and $z = 36$. To test the hypothesis that the dACC showed additive activity when cognitively and emotionally aversive cues were combined, we obtained the percentage signal change using Marsbar software (Brett et al., 2002). It should be noted that we used a factorial design for the whole brain analysis, but the extracted data were analyzed using a one-way ANOVA with four levels (Pain-Short, Pain-Long, No Pain-Short, No Pain-Long) to observe the combined aversive cue (i.e., Pain-Short) induced additive activation relative to the single cues (i.e., Pain-Long, and No Pain-Short). Based on these results, the dACC showed the greatest activity when cognitively and emotionally aversive cues were contiguously presented (Fig. 6, bottom). It was also shown that cognitively or emotionally aversive cues produced greater dACC activation than did the baseline condition (Fig. 6, bottom). The ANOVA showed a main effect of the cue condition with four levels ($F_{[1, 3]} = 14.92, p < .001$). A post-hoc multiple

### Table 2. Mean reaction time in each condition in the Stroop-Franker task. SDs are shown in parenthesis.

| Pain       | Short | Incongruent | Long | Incongruent |
|------------|-------|-------------|------|-------------|
|             |       |             |      |             |
| No Pain    |       |             |      |             |
| Short      |       |             |      |             |
| Congruent  | 618.65| (144.52)    | 676.87| (139.99)    |
| Incongruent| 685.91| (138.75)    | 756.65| (141.50)    |
| Congruent  | 643.33| (131.37)    | 727.52| (149.26)    |
| Incongruent| 699.25| (139.97)    | 779.34| (148.72)    |

### Table 3. Mean accuracy in each condition in the Stroop-Franker task. SDs are shown in parenthesis.

| Pain       | Short | Incongruent | Long | Incongruent |
|------------|-------|-------------|------|-------------|
|             |       |             |      |             |
| No Pain    |       |             |      |             |
| Short      |       |             |      |             |
| Congruent  | 96.2  | (7.08)      | 98.2 | (4.45)      |
| Incongruent| 93.7  | (7.60)      | 97.5 | (5.46)      |
| Congruent  | 91.0  | (6.89)      | 97.0 | (3.80)      |
| Incongruent| 93.3  | (8.49)      |       |             |
Comparison analysis showed that the dACC activity of the Pain-Short condition was significantly greater than that of the Pain-Long (p < .001), No Pain-Short (p = .01), and No Pain-Long (p < .001) conditions. The dACC activity was greater in the pain-long condition than in the no pain-long condition (p = .004). Similarly, dACC activity was greater in the No Pain-Short condition than in the No Pain-Long condition (p = .01).

An exclusive mask analysis was used to identify the brain regions specifically activated in the pain conditions, which showed no clusters above the statistical threshold. We performed another exclusive mask analysis to specify the brain regions activated in the time conditions, and the following regions showed greater activation by the time conditions after excluding the effect of the pain: the lateral prefrontal cortex (lPFC), medial frontal cortex, including the supplementary motor area, middle cingulate cortex, posterior parietal cortex, inferior temporal cortex, occipital cortex, cuneus, basal ganglia, insula, thalamus, and cerebellum. The peak coordinates and values are listed in Table 4. Because the medial frontal cortex showed a main effect of time condition, we performed a small volume correction analysis to explore whether some portion of the dACC was specialized in processing a cognitively aversive cue. As a result, a superior cluster of the dACC (-6, 4, 40) showed selective activation in response to the short-time-window cue (Fig. 7).

**Psycho-physiological interaction results**

For the pain conditions, the dACC was strongly coupled with the posterior occipital cortices compared with the no-pain condition (Fig. 8, left). The specific coordinates and values are listed in Table 5. For the short-time-window conditions, the dACC was strongly coupled with various brain regions relative to the long-time-window conditions (Fig. 8, right). These include the medial frontal cortex (supplementary motor area and middle cingulate gyrus), posterior parietal and occipital cortices, inferior temporal gyrus, basal ganglia, insula, thalamus, and cerebellum. The functional coupling was also found in the brainstem regions, including the ventral tegmental area (VTA) and locus coeruleus (LC) (Fig. 9). The specific coordinates and values are listed in Table 6.

As reported above, the dACC is coupled with the posterior occipital cortices under painful conditions. Considering that the dACC is known to be activated by attention, dACC activity merely reflects attentional demand rather than cognitive control. To test the hypothesis, we examined whether the dorsal attentional network (DNT) regions showed similar activation to the dACC. For the analysis, we performed small volume correction analyses using two ROIs: DNT anterior and DNT posterior. Those ROIs were selected, referring to the previous study (Spreng et al., 2013). The DNT anterior covered the bilateral frontal eye field (FEF) and inferior precentral sulcus (iPCS), and the DNT posterior did the bilateral middle temporal motion complex (MT), superior occipital gyrus (SOG), and the superior parietal lobule (SPL). As with the dACC, we first created a total of 10 sphere masks with 20 mm radius, and each central coordinate was retrieved from the previous study (Table 1 in Spreng et al., 2013). The FEF mask was created by overlapping the sphere image and the MNI_Frontal_Mid of the AAL structure image in each hemisphere. Similarly, the other masks were created, using the following AAL images: MNI_Postcentral for the iPCS, MNI_Temporal_Mid for the MT, MNI_Occipital_Sup for the SOG, and MNI_Parietal_Sup for the SPL. Finally, we created the DNT anterior mask (Supplementary Fig. 1) by combining the FEF and iPCS, and the DNT posterior mask (Supplementary Fig. 2) by the MT, SOG and SPL. We focused on the two masks to minimize Type-I error due to repetitive comparisons. Each mask was applied to the conjunction activation maps (i.e., main effects of the pain and time) for small volume correction analyses. The results showed no voxles that satisfied the statistical threshold (p < .05, FWE corrected for multiple comparisons). Those provide one evidence that the dACC activity obtained in the present study is not simply associated with attentional demand, but is involved in cognitive control.
Neural-behavior relationship

To examine the relationships between neuronal and behavioral data, we extracted the beta-weighted values of the dACC commonly activated in response to cognitively and emotionally aversive cues. We also extracted the beta-weighted values of the regions that were effectively connected with the dACC, as shown in Tables 5 and 6. A sphere with a radius of 4 mm was created for each ROI, and each central coordinate is listed in Tables 5 and 6. Pearson’s correlation analysis was used to determine the correlations between beta-weighted values and behavioral data. Bonferroni’s procedure was applied for multiple comparisons of the PPI data.

The activity of the dACC was negatively correlated with reaction time, especially for the most aversive condition (Pain-Short condition), as shown in Fig. 10 (top-left). For task accuracy, dACC activity showed a trend toward a significant positive correlation ($r = 0.36, p = .06$ for the Pain-Short condition; $r = 0.35, p = .06$ for the No Pain-Short condition, and $r = 0.32, p = .09$ for the No Pain-Long condition). A significant positive correlation was observed for the Pain-Long condition ($r = 0.39, p = .04$). These results suggest that subsequent task performance was modulated by dACC activity during the cue phase, which may reflect adjusted control signals for adaptive behaviors.

For effective connectivity that was strongly coupled with the dACC under emotionally aversive conditions (i.e., pain conditions), the beta-weighted value of the left visual cortex was negatively correlated with reaction time (Fig. 11, right). This correlation was not observed in the right visual cortex (Fig. 11, left). Regarding effective connectivity under cognitively aversive conditions (i.e., short conditions), no regions survived after correcting the $p$-value.

Multiple regression analysis including state-anxiety level

An additional multiple regression analysis was performed to determine whether dACC activity was related to
emotional aversiveness. For the analysis, we focused on dACC activity in the pain-long condition (emotionally aversive) and the no-pain short condition (cognitively aversive). In the analysis, we included mean reaction time data for each condition and state anxiety level as an independent variable, and dACC activity as a dependent variable.

In the long-pain condition, the analysis yielded a significant multiple regression coefficient, $F(2, 25) = 4.01, p < .05$, and each independent variable (i.e., reaction time and state anxiety score) significantly predicted the activity of the dACC (Table 7). On the other hand, such a significant multiple regression coefficient was not obtained in the no-pain short condition, $F(2, 25) = 3.09, p > .05$ (Table 8).

**DISCUSSION**

The present study tested the hypotheses that (a) the dACC is commonly activated in response to the emotionally aversive cue.

**Table 5.** Regions effectively connected with the dACC in the pain conditions.

| Region                     | L/R | x   | y   | z   | BA | Cluster | T-value |
|----------------------------|-----|-----|-----|-----|-----|---------|---------|
| Inferior Occipital Gyrus   | R   | 36  | -90 | 0   | 19  | 306     | 5.77    |
| Lingual Gyrus              | R   | 22  | -92 | -10 | 18  | 3.79    |
| Inferior Occipital Gyrus   | L   | -24 | -90 | -8  | 18  | 596     | 5.16    |
| Calcarine Gyrus            | L   | -18 | -100| -2  | 17  | 4.63    |
| Middle Occipital Gyrus     | L   | -32 | -94 | 2   | 18  | 4.54    |

**Fig. 8.** Regions effectively connected with the dorsal anterior cingulate cortex under pain conditions relative to the no-pain conditions (Left). Regions effectively connected with the dorsal anterior cingulate cortex under the short-time window conditions relative to the long-time window conditions (Right).

**Fig. 9.** The brainstem regions effectively connected with the dACC in response to the cognitively aversive cue. The red circles in the left panel indicate the ventral tegmental area, and that in the right indicates the locus coeruleus.
The EDA analysis showed that both cognitive and emotional cues provoked arousal responses potentially associated with aversiveness. In the present task, a cognitively aversive cue that required a quick response will require precise trigger manipulation. However, for any reason, the trigger output could be delayed, meaning that the trigger was received by the EDA recording device.

Once the cue was presented, the experimental program was set to produce a trigger that was sent to the EDA recording device. This caused the EDA device to produce a trigger that was sent to the EDA recording device. This caused the EDA device to produce a trigger that was sent to the EDA recording device. This caused the EDA device to produce a trigger that was sent to the EDA recording device. This caused the EDA device to produce a trigger that was sent to the EDA recording device. This caused the EDA device to produce a trigger that was sent to the EDA recording device. This caused the EDA device to produce a trigger that was sent to the EDA recording device.

Table 6. Regions effectively connected with the dACC in the short time window conditions.

| Region                           | L/R | x   | y   | z   | BA | Cluster | T-value |
|---------------------------------|-----|-----|-----|-----|-----|---------|---------|
| Supplementary Motor Area        | L   | −10 | 10  | 56  | 6   | 395     | 4.52    |
| Middle Cingulate Gyrus          | L   | −12 | 10  | 44  | 32  |         | 4.25    |
| Inferior Parietal Sulcus        | L   | −32 | −50 | 50  | 40  | 1315    | 5.95    |
| Middle Occipital Sulcus         | L   | −22 | −60 | 40  | 7   | 5.35    |         |
| Lingual Gyrus                   | L   | −26 | −94 | −14 | 18  | 4637    | 6.09    |
| Cerebellum                      | L   | −30 | −76 | −28 |    |         | 3.66    |
| Cerebellum                      | L    | 38 | −62 | −24 |    |         | 3.84    |
| Calcarine Gyrus                 | L   | −14 | −98 | −10 | 18  |         | 5.74    |
| Superior Occipital Gyrus        | R   | 30  | −60 | 30  | 19  | 538     | 4.7     |
| Inferior Parietal Sulcus        | R   | 30  | −54 | 50  | 7   | 3.54    |         |
| Angular Gyrus                   | R   | 28  | −58 | 50  | 7   | 4.47    |         |
| Fusiform Gyrus                  | R   | 38  | −60 | −10 | 37  | 3.85    |         |
| Middle Occipital Sulcus         | R   | 32  | −70 | 26  | 19  | 4.24    |         |
| middle Cingulate Gyrus          | R   | 16  | −46 | 34  | n/a | 819     | 5.08    |
| Cuneus                          | R   | 10  | −72 | 36  | 7   | 4.91    |         |
| Precuneus                       | R   | 6   | −66 | 40  | 7   | 4.82    |         |
| Caudate                         | R   | 22  | 26  | 8   | n/a | 8378    | 6.45    |
| Caudate                         | L   | −16 | 26  | 10  | n/a | 3.91    |         |
| Pallidum                        | R   | 14  | 2   | 2   | n/a | 5.43    |         |
| Pallidum                        | L   | −16 | 2   | 4   | n/a | 3.5     |         |
| Thalamus                        | R   | 6   | −14 | 8   | n/a | 4.36    |         |
| Thalamus                        | L   | −12 | −18 | 4   | n/a | 5.42    |         |
| Insula                          | L   | −28 | 32  | 10  | n/a | 4.77    |         |
| Fusiform Gyrus                  | L   | −36 | −28 | −14 | 20  | 3.83    |         |
| Brain Stem Regions              |     |     |     |     |     |         |         |
| Ventral Tegmental Area          | L   | −4  | −16 | −12 | n/a | 4.35    |         |
| Ventral Tegmental Area          | R   | −4  | −16 | −12 | n/a | 4.13    |         |
| Locus Coeruleus                | L   | −6  | −36 | −34 | n/a | 3.43    |         |
| Locus Coeruleus                | R   | 4   | −32 | −20 | n/a | 3.47    |         |
pattern of activity depending on the task demand. Although we interpreted the activity of the dACC as a neural response to cognitively and emotionally aversive cues, it is still possible that the activity reflects different types of cognitive demand (accuracy and speed). Multiple regression analyses were performed, including individual state anxiety during the task, to determine whether dACC activity contains neural responses related to negative emotions. Interestingly, in response to the emotionally aversive cue (i.e., Pain-Long condition), the dACC activity was predicted by reaction time and individual state anxiety score; however, this result was not obtained in response to the cognitively aversive cue (i.e., No-Pain Short condition). This result agrees with our interpretation that dACC activity is modulated by the fear of pain. Although the results provide indirect evidence, and further elaborative investigations are required, the dACC activity observed in the present study may contain neural responses related to negative emotions.

Conjunction analysis showed overlapping activity in a portion of the dACC (x = 14, y = 14, z = 36) in response to cognitively and emotionally aversive cues. This result supports the general function of the dACC in processing...
various aversive stimuli, which allows organisms to switch their behavior towards adaptive stimuli (Shackman et al., 2011). More importantly, when the activity of the dACC was further analyzed using ROI analysis, a combination of two aversive cues yielded an additive response of the dACC. This result further supports the general responsiveness of the dACC to aversive information, possibly by integrating two different types of aversive information to facilitate a quick behavior change to avoid undesired outcomes. The activities of the dACC under the pain-only and short-time window conditions were also comparable, and they were greater than that of the no-aversive condition where a participant could perform the Stroop-Flanker task without fear of pain and a slow time window. Taken together, the conjunction analysis and further ROI analysis consistently supported the general responsiveness hypothesis for the dACC. Although we briefly propose an integrative account of the dACC for adaptive behavioral shifts in the context of multiple aversive stimuli, the additive activity merely reflects the overlapped repre-

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**Table 7.** Result of the multiple regression analysis in the pain long condition.

| Coefficients | Estimate  | Std.Error  | t-value  | Pr(>|t|)  |
|--------------|-----------|------------|----------|-----------|
| (Intercept)  | 1.957026  | 0.599195   | 3.266    | 0.00316   |
| RT in Pain Long | -0.00131  | 0.000538   | -2.44    | 0.02212   |
| State AI    | -0.02139  | 0.010074   | -2.123   | 0.04382   |

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.3661 on 25 degrees of freedom
Multiple R-squared: 0.2453, Adjusted R-squared: 0.1849
F-statistic: 4.062 on 2 and 25 DF, p-value: 0.02968

**Table 8.** Result of the multiple regression analysis in the pain long condition in the no-pain short condition.

| Coefficients | Estimate  | Std.Error  | t-value  | Pr(>|t|)  |
|--------------|-----------|------------|----------|-----------|
| (Intercept)  | 1.716987  | 0.582625   | 2.947    | 0.00686   |
| RT in No_Pain Short | -0.0011   | 0.000584   | -1.883   | 0.07139   |
| State AI    | -0.01957  | 0.011035   | -1.773   | 0.08837   |

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 0.418 on 25 degrees of freedom
Multiple R-squared: 0.2453, Adjusted R-squared: 0.1849
F-statistic: 3.095 on 2 and 25 DF, p-value: 0.02968
sentation shared by distinctive aversive information. Further studies are required to elucidate the integrative nature of the dACC.

The general responsiveness of the dACC can be extended to any type of motivational information. According to the expected value of control theory (Shenhav et al., 2013; Shenhav et al., 2016), the dACC modulates cognitive control signals by integrating positive and negative outcomes. Similarly, the reinforcement learning model of the dACC is also proposed to learn both affectively positive and negative outcomes (Silvetti et al., 2014). Using a cueing paradigm, Vassena et al. (Vassena et al., 2014) separately presented a high-reward and a high-effort cue. When applying conjunction analysis, the authors found that the dACC commonly responded to incentive and cognitively challenging cues.

A more recent study tested the hypothesis that the dACC integrates primary and secondary motivational cues for behavioral adjustment (Yee et al., 2021). The authors computationally quantified the values of the combined reward (i.e., liquid valence and monetary amount) and searched for brain regions that correlated with the values. In the focused ROI analysis, the combined values successfully predicted the dACC activity. The findings not only suggest that the dACC is responsive to two different types of motivational cues but also integrate them to modulate cognitive control signals. A similar integrative account was proposed in a previous study (Krebs et al., 2012). This account may be applied to the present finding that the dACC showed additive activity when the two aversive cues were combined. Future studies are expected to meticulously examine the integrative account, as well as the hypothesis that the dACC is responsive to any type of motivational signal to modulate behavioral adaptations.

When attempting to interpret the present findings from a neurocomputational perspective, the RML model seems to be the most optimal selection. In the RML model, the dACC and brainstem neurotransmitter systems optimally modulate the learning rate, reward, and effort, and their interaction allows for autonomous flexibility to manage the changing demands in cognitive control (Silvetti et al., 2018). Given that cells in the dACC code values of environmental states, increased dACC activity in response to cognitively affectively aversive cues may indicate negative values associated with those cues. Furthermore, the dACC modulates the release of catecholamines from the brainstem nuclei (LC and VTA) to generate control signals based on task demands. In agreement with this proposal, when quick responses were demanded by the cognitively aversive cues, the dACC showed stronger effective connectivity with the brainstem regions, including the VTA and LC. It should also be noted that tonic LC activity is correlated with the sympathetic nervous system, which is reflected as an increase in pupil diameter, heart rate, and galvanic skin response (Wang et al., 2018). The EDA increments observed in the present study may indicate LC activity modulated by the dACC. Collectively, the dACC seems not only to flexibly code the values of environmental cues but also to interact with the brainstem neurotransmitter systems to adjust to the volatile environment.

Complementary correlation analyses of dACC activity and task performance revealed a negative correlation between dACC activity and reaction time and a positive correlation between dACC activity and accuracy, especially under the most aversive conditions (i.e., Pain-Short condition). Participants with greater dACC activity showed better performance, especially when cognitively and emotionally aversive cues were presented contiguously. These results support our interpretation of dACC activity as a control signal produced to regulate behavior in a volatile environment (Shenhav et al., 2013; Silvetti et al., 2014; Shenhav et al., 2016; Silvestrini et al., 2022). As this region is predicted to exert its effect on other brain regions to generate an appropriate response depending on the task demand, we further performed an effective connectivity analysis to investigate the mechanism underlying the control of the dACC. Under painful conditions, the dACC is functionally coupled with the posterior occipital cortices. This result can be interpreted as top-down control by the dACC to enhance the detection of the following target stimuli by upregulating the activity of the posterior occipital cortices, as reported in previous studies (Roelfsema et al., 1998). Additional preliminary correlation analyses showed a negative correlation between the reaction time and neural coupling between the dACC and left occipital visual cortices. This also supports our interpretation of top-down regulation by the dACC. The absence of a significant correlation in the right visual cortex may be due to its dominant functions, such as emotional and global processing, which may mask individual differences in top-down attentional control (Moreno et al., 1990; Evans et al., 2000). Under short-time-window conditions, the dACC was functionally coupled with the medial frontal cortex, posterior parietal cortices, medial parietal cortices, inferior temporal cortices, posterior occipital cortices, basal ganglia, thalamus, and cerebellum. The dACC may affect motor-related regions, such as the medial frontal cortex (Narayanan and Laubach, 2006), basal ganglia (Nambu et al., 2002), and cerebellum (Zackowski et al., 2002), to promote prompt motor response to a subsequent target. Selective attention may be enhanced by a signal from the dACC to the posterior parietal (Corbetta et al., 2000), inferior temporal (Desimone and Duncan, 1995), and occipital cortices (Gandhi et al., 1999) and the thalamus (Rafal and Posner, 1987), as reported in previous studies.

The dACC did not seem to affect the activity of the IPFC, although an exclusive mask analysis showed activity of the region under short-time-window conditions (Table 4). It is widely believed that the IPFC holds task-related information in the working memory (Miller et al., 1998) and controls other brain structures in a top-down manner (Gazzaley et al., 2005). The absence of effective connectivity from the dACC to the IPFC may indicate that each region exerts its effects on the motor and sensory regions through separate neural pathways. Further studies are required to investigate the characteristics of neural
pathways from the dACC and IPFC to other neural structures in humans.

Finally, exclusive mask analyses showed that the superior part of the dACC (-6, 4, 40) was uniquely activated in response to cognitively aversive cues. The superior dACC was reported to be activated in cognitive conflict but not in pain (Jahn et al., 2016), indicating that the present result may reflect preparation for upcoming cognitive conflict under a short response window. In contrast, we found no particular dACC loci for emotionally aversive cues. These findings partially support the functional segregation of the dACC. Collectively, our results suggest that the specific locus of the dACC is generally responsive to motivational information, whereas other loci have distinctive functions. Further studies using sophisticated experimental methods are required.

In conclusion, the present study showed that a specific locus of the dACC region is responsive to multiple types of aversive information, which results in the adjustment of a control signal toward the sensorimotor regions. In addition, as proposed by many theories, the dACC exerts its effect on other brain structures, possibly producing and delivering control signals depending on the task demand.

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APPENDIX A. SUPPLEMENTARY MATERIAL

Supplementary material to this article can be found online at https://doi.org/10.1016/j.neuroscience.2022.09.001.