Primary Interoceptive Cortex Activity during Simulated Experiences of the Body

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Abstract

■ Studies of the classic exteroceptive sensory systems (e.g., vision, touch) consistently demonstrate that vividly imagining a sensory experience of the world—simulating it—is associated with increased activity in the corresponding primary sensory cortex. We hypothesized, analogously, that simulating internal bodily sensations would be associated with increased neural activity in primary interoceptive cortex. An immersive, language-based mental imagery paradigm was used to test this hypothesis (e.g., imagine your heart pounding during a roller coaster ride, your face drenched in sweat during a workout). During two neuroimaging experiments, participants listened to vividly described situations and imagined "being there" in each scenario. In Study 1, we observed significantly heightened activity in primary interoceptive cortex (of dorsal posterior insula) during imagined experiences involving vivid internal sensations. This effect was specific to interoceptive simulation: It was not observed during a separate affect focus condition in Study 1 nor during an independent Study 2 that did not involve detailed simulation of internal sensations (instead involving simulation of other sensory experiences). These findings underscore the large-scale predictive architecture of the brain and reveal that words can be powerful drivers of bodily experiences. ■

INTRODUCTION

Imagine gazing down the dramatic slope of a seaside cliff as cool blasts of invigoratingly salty air whip across your face. Words come alive when they appeal to the senses, and neuroscience is revealing why. Studies of the classic exteroceptive sensory systems (e.g., vision, touch, smell) consistently show that vividly imagining a sensory experience implements a pattern of neural activity in the corresponding primary sensory cortex (McNorgan, 2012; Kosslyn, Ganis, & Thompson, 2001). These findings demonstrate that top–down simulations penetrate into the primary sensory cortices. One sensory system is noticeably absent in this literature, however: interoception. Interoception refers to sensing the physiological condition of the body; primary interoceptive cortex in dorsal posterior insula receives sensory input from the body's internal milieu (Nieuwenhuys, 2012; Craig, 2002). Here, we present evidence that the interoceptive system functions analogously to the exteroceptive systems: Simulating internal bodily sensations during a vividly imagined experience implements a pattern of neural activity in primary interoceptive cortex. Return to the wildly windy cliff for a moment, and imagine that a sudden and gripping chill ripples through your body. You shiver. Your stomach tightens. Your breath quickens. In this study, we examined how words construct bodily experiences through simulation.

Recent theoretical advances propose that conceptually driven, top–down processing occurs in the brain's interoceptive system because interoceptive functioning is grounded in general principles that apply across sensory systems (Kleckner et al., 2017; Chanes & Barrett, 2016; Seth & Friston, 2016; Barrett & Simmons, 2015; Farb et al., 2015; Pezzulo, Rigoli, & Friston, 2015; Seth, 2013). The Embodied Predictive Interoceptive Coding (EPIC) model, in particular, specifies a neuroanatomical, computational framework in which top–down simulations of bodily sensations are represented throughout the interoceptive system, including in primary interoceptive cortex (Barrett, 2017; Chanes & Barrett, 2016; Barrett & Simmons, 2015). In the same way that the sensory details of exteroceptive simulations are implemented in the primary sensory cortices (McNorgan, 2012), such as implementing simulations of visual details in primary visual cortex, we hypothesized that the details of interoceptive simulations are implemented in primary interoceptive cortex. Previous research suggests that precise, fine-grained simulations are associated with activity in the corresponding primary sensory cortex (Bergmann, Genc, Kohler, Singer, & Pearson, 2016; Kosslyn & Thompson, 2003).

Specifically, we hypothesized that simulating internal bodily sensations within real-world scenarios, foregrounding situation-specific, fine-grained sensory details (e.g., imagining your heart pounding during a roller coaster

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ride, sweat dripping from your face during a workout), would be associated with increased neural activity in primary interoceptive cortex of dorsal posterior insula. Immersive mental imagery guided by precise language is an ideal paradigm for examining top–down interoceptive simulation in the brain and, more generally, the neural correlates of a capacity that is central to human experience. Projecting oneself into a different situation, referred to here as scenario immersion, is involved in preparing for the future, reliving the past, taking another's perspective, or simply escaping the present (Pearson, Naselaris, Holmes, & Kosslyn, 2015; Moulton & Kosslyn, 2009; Buckner & Carroll, 2007).

We investigated the interoceptive simulation hypothesis through archival analyses of two published neuroimaging experiments (Wilson-Mendenhall, Barrett, & Barsalou, 2013a; Wilson-Mendenhall, Barrett, Simmons, & Barsalou, 2011). Both studies involved a scenario immersion procedure designed to maximize ecological validity: Participants listened with eyes closed to scenarios rich in multimodal sensory details and imagined "being there" in each scenario as if it was actually happening to them. A comprehensive analysis approach across the two studies supported testing the interoceptive simulation hypothesis, which included within-subject and between-subject statistical tests. In Study 1, scenario immersion foregrounded bodily sensations and thus provided a key test of the hypothesis that top–down interoceptive simulation is associated with heightened activity in primary interoceptive cortex. Further analyses examined specificity. Study 1's design provided an active comparison condition for within-subject analysis. On most trials in Study 1, scenario immersion was followed by a subsequent affect focus phase in which participants focused on affective feelings emerging in the scenario. Analogous to the literature demonstrating that precise, fine-grained visual simulations are associated with activity in primary visual cortex (Bergmann et al., 2016; Kosslyn & Thompson, 2003), we hypothesized that activity in primary interoceptive cortex would be greater during scenario immersion involving fine-grained simulations of bodily sensations than during coarse-grained affective focus, in which bodily sensations were experienced with less precision as affective feelings. Study 2 provided an additional, between-subject test of the interoceptive simulation hypothesis. In Study 2, scenario immersion did not involve fine-grained simulation of internal sensations (instead foregrounding other sensory details) and thus offered a further test of whether heightened primary interoceptive cortex activity during Study 1 scenario immersion was specific to interoceptive simulation.

METHODS

Because comprehensive design details are available for Study 1 (Wilson-Mendenhall et al., 2013a) and Study 2 (Wilson-Mendenhall et al., 2011) in published articles that examine different hypotheses, we focus on the methods and analysis approach that address the novel hypotheses presented here.

Participants

Native English speakers with no history of psychiatric illness constituted both samples. Study 1 participants ($n = 16$, eight women) ranged in age from 19 to 30 years, and Study 2 participants ($n = 20$, 10 women) ranged in age from 20 to 33 years.

Procedural Overview

Both studies induced affective feelings through immersion in scenarios depicting real-world experiences. An initial training session occurred 24–48 hr before a second refresher session, which occurred just before the scan session. Full paragraph-long forms of each scenario provided a richly detailed immersion experience during the training sessions. A corresponding shorter, core form of each scenario served to minimize presentation time in the scanner so the number of trials necessary for a powerful design could be implemented. During the first training session, participants practiced immersing in full versions of the scenarios and reinstating imagined details from the full versions upon immersing in the core forms (see Wilson-Mendenhall et al., 2011, 2013a, for details). In the second refresher session occurring just before imaging, participants immersed in the full versions again to ensure they were reacquainted with scenario details before the scan session in which the core forms were presented.

Scenario Stimuli

Because Study 1 and Study 2 scenarios were initially developed for two different studies that tested unique hypotheses (Wilson-Mendenhall et al., 2011, 2013a), we computed an objective measure of interoceptive content, which is the between-subject manipulation of interest here. We expected that automated text analysis would show that Study 1 scenarios contained more interoceptive content than Study 2 scenarios. After describing the construction and content of the scenarios, we present the results of this analysis.

In both studies, scenario templates defined a standard sentence structure and specified general content, with the specific situational details varying across scenarios. Table 1 provides example scenarios, and the scenario templates are available in the Appendix. The scenarios in both studies were second-person narratives designed to induce an affective experience (e.g., you feel… you're…). Participants listened to the audio recordings of the scenarios with eyes closed to facilitate immersion. In both studies, scenario templates specified an affective

Table 1. Example Study 1 and Study 2 Scenarios

Study 1	*Study 2*
You are sitting home alone reading, immersed in a dramatic murder mystery. You startle violently when you hear the piercing sound of glass breaking. *Launching out of your chair, your heart is palpitating wildly in your chest.* Your mind harbors terrible visions of your assailant as you grab for the phone. You feel a striking fear.	You're jogging along an isolated lake at dusk. Thick dark woods surround you as you move along the main well-marked trail. On a whim, you veer onto an overgrown unmarked trail. You become lost in the dark. The trees close in around you, and you cannot see the sky. You feel your pace quicken as you try to run out of the darkness.
You are playing outside with your nephew, running around tirelessly. You rake up a leaf pile and then take turns jumping in the heap. *You find yourself quickly out of breath from jumping and laughing.* You rapidly forget about being a grown-up and surrender to youthful fun. You feel an enlivening happiness.	You're at a dinner party with friends. A debate about a contentious issue arises that gets everyone at the table talking. You alone bravely defend the unpopular view. Your comments are met with sudden uncomfortable silence. Your friends are looking down at their plates, avoiding eye contact with you. You feel your chest tighten.

Italics in Study 1 indicate focal interoceptive detail.

event and provided sensory details that elaborated the event (see Table 1 and Appendix).

Study 1 scenarios were designed to induce multisensory affective experiences. Each scenario was five sentences long, with one sentence focused exclusively on describing bodily changes. This sentence referred to sensory changes occurring in the body during the affect-inducing event (e.g., your heart is pounding, you take a deep breath, sweat drips off your face, your muscles unwind and loosen). The specific interoceptive details are provided in the Appendix. Furthermore, an internal orientation to body and mind was present throughout the scenario. Each scenario opened by describing the state of the body, elaborated the affective feelings generated by a key event, and closed by describing the experience as a particular emotion. The scenarios varied in emotional valence and arousal to test an initial hypothesis (Wilson-Mendenhall et al., 2013a). This design was advantageous here because it induced immersive, contextually grounded interoceptive imagery and thus provided repeated sampling of interoceptive simulation in the scenarios.

Study 2 scenarios were similarly designed to induce multisensory affective experiences. Each scenario was six sentences long and, in contrast to Study 1 scenarios, were primarily externally focused. Scenarios opened with a focus on the setting and activity and subsequently moved into elaboration of a visual or auditory detail. The description of the affective event focused on action and the consequence of that action. In some cases, the scenario ended with a brief bodily detail, but as the objective measure described next indicates, this was minor in comparison with Study 1. Because the first hypothesis examined with this study investigated situational context, the scenario events were either a physical danger or social evaluation theme (Table 1 provides an example of each theme; Wilson-Mendenhall et al., 2011).

Differences between the language-based scenarios in the two studies were quantified using an objective measure generated by the text analysis software LIWC (Tausczik & Pennebaker, 2010). LIWC calculates the proportion of words in a text sample that fall in a content category, which is defined by a list of words. We created two new LIWC categories, Internal Body and Body Parts, by selecting words from the existing (and broad) LIWC categories Affect, Bio, Body, and Health. Neuroanatomical descriptions of the interoception system (Nieuwenhuys, 2012; Craig, 2002) guided construction of the Internal Body category. The 208 words in this category referred to the physiological condition of the body and included somatovisceral sensations (e.g., hunger, breath); pain (e.g., headache, cramp); somatic symptoms (e.g., cough, fever); and internal organs, glands, and muscles (e.g., stomach, heart). An additional 15 words (7% of total) were added from other sources (e.g., gas, palpitate), including the Body Sensations Questionnaire (Chambless, Caputo, Bright, & Gallagher, 1984), Body Vigilance Scale (Schmidt, Lerew, & Trakowski, 1997), and Patient Health Questionnaire-15 (Kroenke, Spitzer, & Williams, 2002). Body Parts provided a contrasting "body" category that included 107 words referring to different parts of the body (e.g., arm, hip).

The proportions of Internal Body and Body Parts words in the scenarios from Study 1 ($n = 90$) and Study 2 ($n = 60$) deviated significantly from a normal distribution (Kolmogorov–Smirnov $p < .05$) and could not be corrected with outlier removal or log transform (Supplementary Figure 5[1]). Thus, we transformed the data to ranks and conducted nonparametric Mann–Whitney U tests. As expected, Study 1 scenarios contained a significantly higher proportion of internal body words than Study 2 scenarios ($U = 2012, n_1 = 90, n_2 = 60, z = -2.66, p = .01$). The difference was specific to words describing internal sensations; the proportion of general body part words (e.g., arm, leg) did not differ in the two studies ($U = 2696, z = -0.02, p = .99$). We display these results using means and standard errors in Figure 3B, alongside the corresponding imaging results, because these descriptive statistics offered a scale that is readily interpretable while still reflecting the pattern in the transformed rank data.

Image Acquisition and Preprocessing

The functional run scan sequences were identical in the two studies, with the exception of the head coil (Siemens 32-channel head coil used in Study 1 vs. Siemens 12-channel head coil used in Study 2). T2*-weighted echo-planar image volumes depicting BOLD contrast were collected using parallel imaging with an iPAT acceleration factor of 2 (2 mm axial slices, repetition time = 3000 msec, echo time = 30 msec, flip angle = 90°, bandwidth = 2442 Hz/pixel, field of view = 220 mm, matrix = 64, voxel size = 3.44 mm × 3.44 mm × 2 mm). Because the head coils differed, we examined temporal signal-to-noise ratio (TSNR) in the two studies. A TSNR of 40 is recommended to reliably detect effects between conditions in fMRI data (Simmons, Reddish, Bellgowan, & Martin, 2010; Murphy, Bodurka, & Bandettini, 2007). Average TSNR in Study 1 and Study 2 surpassed this threshold in the posterior insula ROIs used to test key hypotheses (details of the 6-mm radius spherical ROIs are presented later in the analysis section; right sphere center 36 −32 16, left sphere center −34 −20 18).

In both studies, standard preprocessing conducted in AFNI software included slice time correction, motion correction, spatial smoothing (6 mm FWHM Gaussian kernel), and percent signal change normalization of each run (in which signal intensities in each volume were divided by the mean signal value for the respective run and multiplied by 100; Cox, 1996). We adjusted the previously reported preprocessing in minor ways to facilitate localization in the insula. First-level regression was computed in native space instead of template space so that we could display individual examples of insula activity (as shown in Figure 2). As reported previously, canonical gamma functions convolved with boxcars reflecting event duration were used to model the hemodynamic response, and six regressors obtained from motion correction during preprocessing were included to remove any residual signal changes correlated with movement (modeling specifics for each study are described in the next sections). The resulting regression coefficients were then warped to Montreal Neurological Institute (MNI) space (instead of Talairach) using the MNI 152 T1-weighted template before group analyses. This procedure facilitated later ROI analyses involving MNI coordinates reported in previous studies.

Study 1 Neuroimaging Design and Analysis

In Study 1, participants immersed in a scenario for 9 sec and then, on most trials, subsequently focused on and rated the induced feeling during a 6-sec affect focus event. Unpredictable trials in which participants immersed in a scenario but did not engage in subsequent affect focus were included so neural activity during scenario immersion could be modeled separately from neural activity during affect focus. These partial "catch" trials accounted for 20% of the 180 total trials (Ollinger, Corbetta, & Shulman, 2001; Ollinger, Shulman, & Corbetta, 2001). Each of six runs consisted of one block of trials in which participants rated arousal during affect focus and one block of trials in which participants rated valence during affect focus (block order counterbalanced across runs; Wilson-Mendenhall et al., 2013a). During each block, 12 complete trials and 3 partial trials were presented in an optimized pseudorandom order amidst jittered resting baseline periods (ranging from 3 to 15 sec in increments of 3 sec).

In individual-level regression analyses, onset times were specified for the scenario immersion events, affect focus events, and the cues beginning blocks. Scenario immersion and affect focus events in arousal blocks were modeled separately from scenario immersion and affect focus events in valence blocks. Because arousal ratings emphasize the body and because the same scenarios were presented in arousal and valence blocks (with only subsequent affect focus differing), the analyses described below were conducted on arousal blocks. Supplementary Figure 6 illustrates that the same robust pattern of results emerged in valence blocks.

Group-level analyses were conducted, first, to examine the hypothesis that top–down interoceptive simulation during scenario immersion foregrounding bodily sensations is associated with heightened activity in posterior insula. Each individual's regression coefficients were entered into group-level analyses conducted within bilateral anatomical masks of the insula (using Eickhoff–Zilles macro labels available in AFNI; Eickhoff et al., 2005; Cox, 1996). One-sample *t* tests examined if scenario immersion differed significantly from the resting baseline using a voxel-wise threshold of $p < .001$. Correction for multiple comparisons within the insula masks was implemented using a corrected $p < .05$ extent threshold of 135 mm^3. AFNI ClustSim's modified procedures address recent criticisms of extent thresholding (Eklund, Nichols, & Knutsson, 2016) by estimating noise smoothness using a spatial autocorrelation function that is fit to a mixed model (Guassian + monoexponential) instead of a pure Gaussian.

To precisely localize primary interoceptive cortex in further analyses, two spheres of 6-mm radius were constructed in dorsal posterior insula from MNI coordinates reported in independent data sets that involved manipulating interoceptive sensation. Coordinates for the sphere in the right dorsal posterior insula (36 −32 16) were drawn from meta-analytic results demonstrating that interoceptive activity in posterior insula was consistently associated with stressor-evoked blood pressure reactivity (Gianaros & Sheu, 2009). Coordinates for the sphere in the left dorsal posterior insula (−34 −20 18) were drawn from a rigorous study that demonstrated, using arterial spin-labeling quantitative perfusion imaging, that interoceptive activity in the left dorsal posterior insula tracks with pain intensity (Segerdahl, Mezue, Okell, Farrar, & Tracey, 2015). We chose to use these coordinates, specifically, because of the lack of available meta-analyses that precisely examine interceptive activity. A recent meta-analysis that examined interoception more broadly, including attention and awareness paradigms (e.g., listening to one's own heartbeat), identified activity in central mid-insula, but not dorsal posterior insula (Kurth, Zilles, Fox, Laird, & Eickhoff, 2010).

We conducted three statistical tests in these ROIs to investigate our a priori hypotheses, implementing a Bonferroni correction for multiple comparisons (resulting in a corrected $p < .01$ threshold). Examination of the distributions of data in each ROI revealed that the distribution of Study 1 scenario immersion coefficients exhibited moderate skew in the right dorsal posterior insula ROI (Kolmogorov–Smirnov $p < .05$). To exercise a conservative approach, we also computed the equivalent nonparametric tests for the right ROI. Because the nonparametric tests yielded the same statistical conclusions as the parametric tests in this ROI, we present the results of the nonparametric analyses in a footnote in the Results section.

The first statistical test replicated the mask analyses within each ROI. We computed one-sample, one-tailed t tests to examine if scenario immersion was significantly greater than resting baseline. The mean of each individual's voxel-wise regression coefficients in the sphere was entered into the t test. The more conservative, nonparametric one-sample Wilcoxon signed-rank test was also computed for the right ROI.

In a first test of functional specificity (and a second statistical test), we capitalized on the catch trial design to compare scenario immersion and affect focus. This contrast allowed us to test the hypothesis that significantly greater activity in primary interoceptive cortex would be observed during scenario immersion involving precise, higher-dimensional simulations of bodily sensations than during affect focus involving less precise, lower-dimensional experiences of bodily sensations. Paired-samples, one-tailed t tests examined if scenario immersion was significantly greater than affect focus in the two independent ROIs. The more conservative, nonparametric Wilcoxon signed-rank test was also computed for the right ROI.

Study 2 Neuroimaging Design and Analysis

Study 2 provided a second crucial test of specificity because, in this study, scenario immersion did not involve detailed simulation of internal bodily sensations. In this study design, participants immersed in a 9-sec social evaluation or physical danger scenario and then, on most trials, subsequently heard one of four possible word cues during a 3-sec event. Each word cue evoked a specific experience within the immersive scenario (e.g., threat-focused fear vs. sensory-focused observation). Unpredictable scenario-only trials were also included in this study, with these partial trials accounting for 33% of the 360 total trials (Ollinger, Corbetta, et al., 2001; Ollinger, Shulman, et al., 2001). During each of 10 runs, 24 complete trials and 12 partial trials were presented in an optimized pseudorandom order amidst jittered baseline periods (ranging from 0 to 12 sec in increments of 3 sec).

Individual-level regression analyses specified onset times for the 9-sec social evaluation and physical danger scenario immersion events. The onset times of the 3-sec cued experience events that followed scenario immersion were also specified (as in Wilson-Mendenhall et al., 2011) but were not examined in any later analyses.

At the group level, we conducted independent, one-tailed t tests in the two dorsal posterior insula ROIs to examine our a priori hypothesis that neural activity during Study 1 scenario immersion would be significantly greater than neural activity during Study 2 scenario immersion, which did not involve detailed simulation of internal sensations. In these tests, we compared Study 1 scenario immersion to the average of the two Study 2 scenario immersion conditions.[2] Equal variances were not assumed due to significant Levene's tests ($p < .05$), and the reported Cohen's d effect sizes are corrected for groups with different sample sizes (d_{Cohen}). The more conservative, nonparametric Mann–Whitney U test was also computed for the right ROI (due to moderate skew in the Study 1 scenario immersion distribution described above).

Parallel to Study 1 analyses, we also conducted an analysis within the bilateral anatomical mask of the insula to examine the possibility that activity in mid-to-posterior insula would be observed outside the spherical ROIs. One-sample t tests examined if scenario immersion differed significantly from baseline in the insula (voxel-wise threshold $p < .001$, corrected $p < .05$ cluster threshold 135 mm^3).

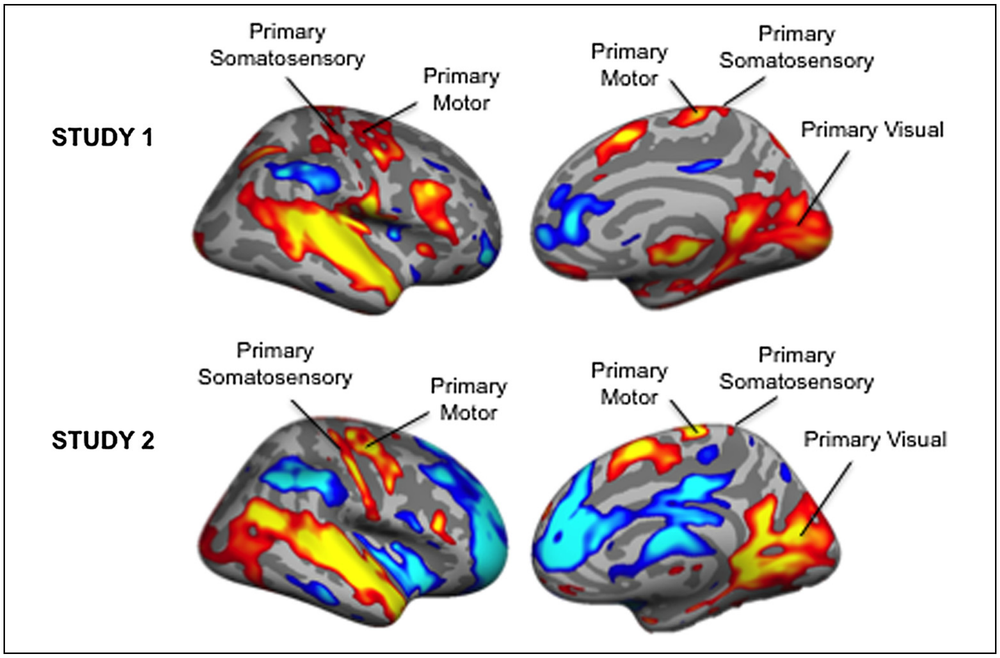
General Whole-brain Approach

Whole-brain analyses of scenario immersion (vs. resting baseline) in both studies were conducted in a gray matter mask of the MNI template. We corrected for multiple comparisons using a false discovery rate (FDR) $q < .05$ (corrected voxel-wise threshold $p < .05$, 20 contiguous voxels).

RESULTS

Heightened neural activity in primary visual, somatosensory, and motor cortices during scenario immersion in both studies replicated prior simulation research (McNorgan, 2012) and established the validity of the paradigm (see also Wilson-Mendenhall, Barrett, & Barsalou, 2013b). Figure 1 illustrates this robust, multimodal neural activity in the whole-brain patterns observed in Study 1

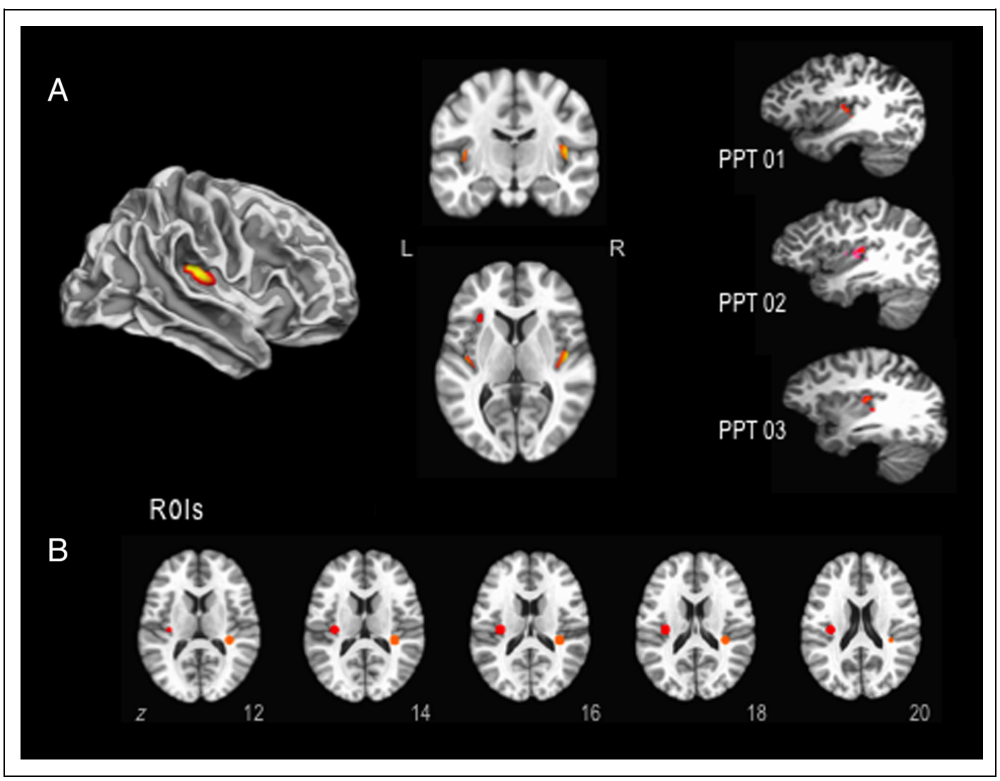
Figure 1. Imagery-based simulation effects replicated across multiple exteroceptive modalities. Study 1 and Study 2 scenario immersion (vs. resting baseline) maps projected on inflated right hemisphere are shown in lateral and medial views. Scenario immersion > baseline in warm colors; scenario immersion < baseline in cool colors. Immersion during Study 2 social evaluation scenarios is shown for conciseness; a very similar pattern emerged across sensory and motor regions during Study 2 physical danger scenarios.



and Study 2 (scenario immersion > resting baseline, corrected $p < .05$).

Study 1 provided the first key test of our hypothesis. Scenario immersion in Study 1 foregrounded the internal bodily changes occurring during the scenario (e.g., stomach queasiness, deep breathing, thumping heart, sweaty palms, relaxing muscles; Wilson-Mendenhall et al., 2013a). Figure 2 illustrates that, as predicted, significantly heightened activity in bilateral, dorsal posterior insula occurred during simulations of internal sensations (scenario immersion > resting baseline, voxel-wise threshold, $t(15) > 4.05$, $p < .001$, corrected $p < .05$ cluster threshold 135 mm^3).

Figure 2. Dorsal posterior insula activity during Study 1 scenario immersion. (A) Group-level results shown in the right hemisphere and in representative axial ($z = 6$) and coronal ($y = -14$) slices (right cluster: 1630 mm^3, center 41 −15 10; left cluster: 854 mm^3, center −38 −19 11). Three examples at the individual level (scenario immersion > baseline, $t > 1.96$, $p < .05$) shown on each individual's anatomy in the right hemisphere, within insula masks generated using Freesurfer's cortical parcellation of each individual's anatomy (Fischl et al., 2004). A cluster in the left anterior insula also emerged in the group-level contrast, which can be seen on the axial slice (616 mm^3, center −30 25 2). (B) Independent ROIs in primary interoceptive cortex that were generated from previous fMRI studies of interoception. The group-level results described in A replicated in these ROIs.



ROI analyses localized this activity in primary interoceptive cortex (Craig, 2002; Nieuwenhuys, 2012). Dorsal posterior insula activity during scenario immersion was significantly greater than resting baseline in the spherical ROIs generated from prior studies investigating interoceptive sensation: (1) ROI based on blood pressure reactivity, $t(15) = 4.30$, $p = .001$, $d = 1.08$[3a] (Gianaros & Sheu, 2009), and (2) ROI based on thermal pain, $t(15) = 5.38$, $p < .001$, $d = 1.35$ (Segerdahl et al., 2015).

Further support for our hypothesis was evident in tests of specificity. Studies of exteroceptive simulation demonstrate that details matter: significant increases in primary visual cortex activity, for example, only occur during simulations rich in visual detail (Kosslyn & Thompson, 2003). A parallel hypothesis was that activity in primary interoceptive cortex would occur during precise, higher-dimensional simulations of bodily sensations and would decrease substantially when bodily sensations are experienced as less precise, lower-dimensional affective feelings. Study 1's design offered a clear test of this hypothesis. After immersing in scenarios rich in interoceptive detail, participants then focused on affective feelings of arousal induced by the scenario. As predicted, Figure 3A illustrates that dorsal posterior insula activity in the independent ROIs was significantly greater during scenario immersion than during subsequent affect focus (right, $t(15) = 3.07$, $p = .004$, $d = .77$[3b]; left, $t(15) = 2.62$, $p = .009$, $d = .66$).

We conducted a second test of specificity in the independent ROIs to examine the hypothesis that the heightened dorsal posterior insula activity observed during Study 1 scenario immersion would not be observed in a second, independent study in which scenario immersion did not involve detailed simulation of internal sensations (Wilson-Mendenhall et al., 2011). As described in the Methods, an objective measure of interoceptive content verified that Study 1 scenarios contained a significantly higher proportion of internal body words than Study 2 scenarios (see Figure 3B, top). Figure 3B illustrates, as predicted, that activity in the independent dorsal posterior insula ROIs was significantly higher during Study 1 scenario immersion (right, $t(16) = 4.41$, $p < .001$, $d_{cohen} = 1.65$[3c]; left, $t(23) = 4.94$, $p < .001$, $d_{cohen} = 1.76$). In Study 2, neural activity during scenario immersion did not differ from within-study baseline resting activity anywhere in the posterior extent of the insula (voxel-wise threshold, $t(19) > 3.86$, $p < .001$, corrected $p < .05$ cluster threshold 135 mm^3).

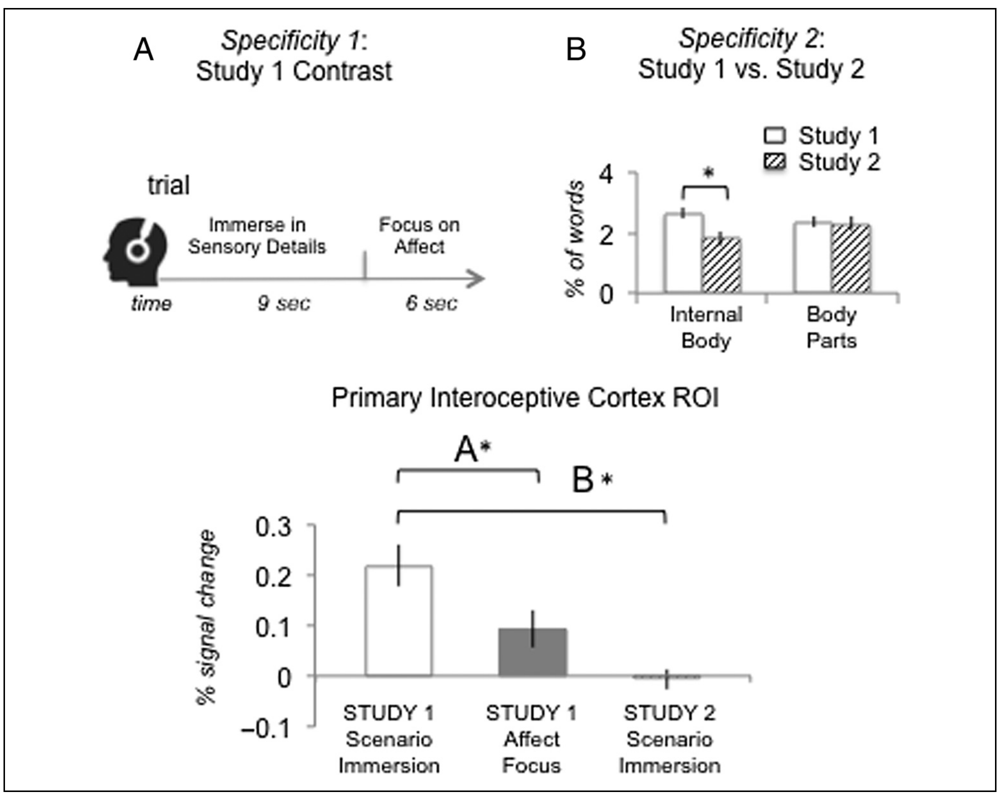


Figure 3. Specificity of dorsal posterior insula activity to interoceptive simulation. Neural activity in the left dorsal posterior insula ROI is displayed. The same pattern of results was observed in the right dorsal posterior insula ROI. Image (A) contrasts Study 1 scenario immersion with Study 1 affect focus. The diagram on the top left illustrates the within-subject design that provided an active comparison condition—affect focus—for this contrast. The significantly greater activity during immersion in precise interoceptive detail versus focus on affect with less interoceptive precision is illustrated below, with the asterisk labeled A. Image (B) contrasts Study 1 scenario immersion with Study 2 scenario immersion. The graph on the top right displays the results of the automated text analysis on the scenarios. Study 1 scenarios contained a significantly greater proportion of internal body words than Study 2 scenarios (but no difference in body part words). Means and standard errors are displayed because these descriptive statistics offer a scale that is readily interpretable while still reflecting the pattern in the transformed rank data of the nonparametric test (we also note that parametric tests in which two extreme values >3 *SD*s were removed showed the same pattern of results as the nonparametric tests, and because means are presented here, we removed these two outliers before visualizing). In the graph below, the asterisk labeled B illustrates the significantly greater activity during Study 1 scenario immersion versus Study 2 scenario immersion. All asterisks are a symbol of $p < .05$.

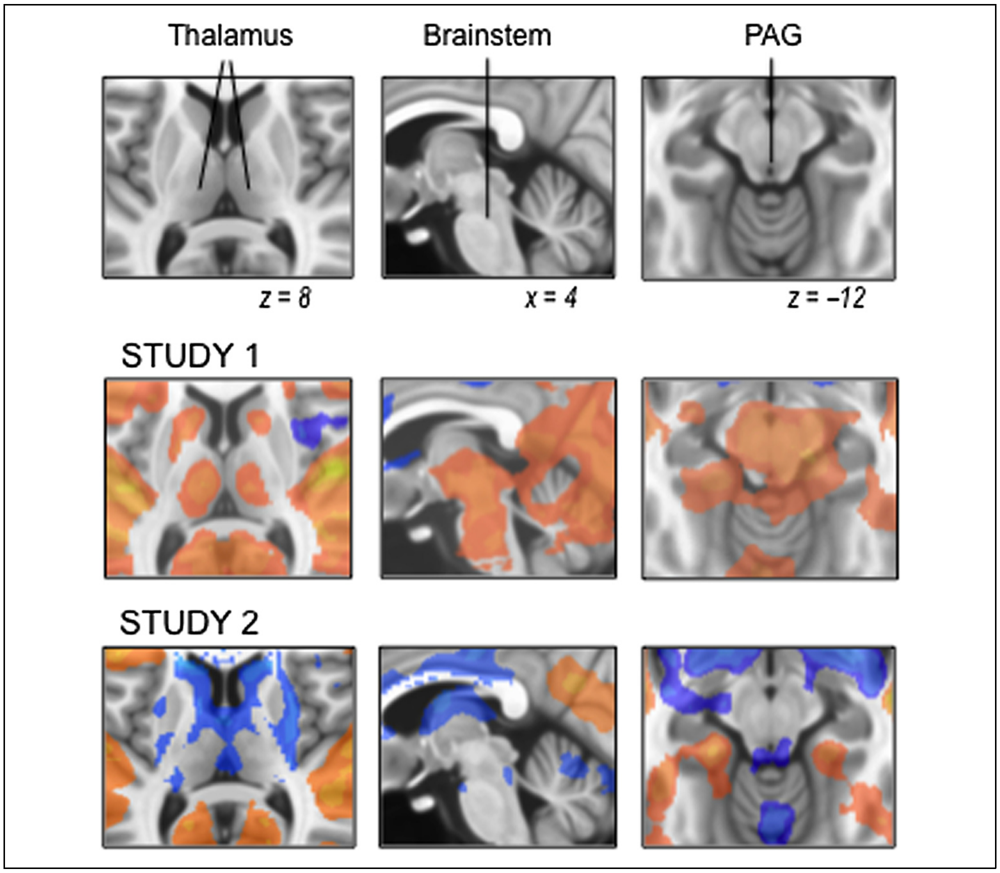


Figure 4. Activity in subcortical regions involved in visceromotor regulation during Study 1 scenario immersion (vs. Study 2 scenario immersion). Scenario immersion > baseline in warm colors; scenario immersion < baseline in cool colors.

Finally, whole-brain analyses provided further evidence of interoceptive simulation. Figure 4 illustrates that top–down simulation of internal sensations reaches deep into subcortical regions of the brain involved in visceromotor regulation (Bar et al., 2016). Significant increases in activity during Study 1 scenario immersion (vs. baseline) occurred in posterolateral thalamus and throughout the brainstem, including the periaqueductal gray, $t(15) > 2.13$, $p < .05$ FDR-corrected. Heightened activity in these regions was not observed during Study 2 scenario immersion, $t(19) > 2.09$, $p < .05$ FDR-corrected.

DISCUSSION

To our knowledge, these studies provide the first evidence that top–down simulations of internal sensations are represented in primary interoceptive cortex. These findings parallel simulation effects observed across the primary sensory cortices of the exteroceptive sensory systems (McNorgan, 2012). Planned analyses across two studies demonstrated the specificity of this result, which was not observed during general affective focus (within-subject results from Study 1) nor during guided immersion that did not involve vivid bodily sensations (between-subject results comparing Study 1 and Study 2). Whole-brain analyses revealing subcortical activity in regions involved in visceromotor regulation provided further support that immersion involving bodily changes engages the interoceptive system.

Simulation in the Interoceptive Sensory Domain

Our results add to accumulating evidence that top–down simulation functions similarly across the different sensory systems, including the interoceptive system. A recent meta-analysis examined imagery in each of the exteroceptive sensory systems (visual, auditory, somatosensory, gustatory, olfactory) and reported evidence of modality-specific neural activity that typically included the corresponding primary sensory cortex (McNorgan, 2012). Using a multimodal immersion paradigm, the results presented here replicated these findings (in the visual and somatosensory domains) and extended them to the interoceptive domain. Over the past decade, rigorous neuroanatomical and neuroimaging studies have characterized a coordinated interoceptive system involved in sensing the physiological condition of the body (Nieuwenhuys, 2012; Stephani, Vaca, Maciunas, Koubeissi, & Lüders, 2011; Craig, 2002, 2003). Our findings highlight that constructing bodily experiences during top–down simulation involves this same system, including primary interoceptive cortex.

Studies of visual imagery suggest that primary visual cortex (V1) is implicated when imagery involves high-resolution visualization of the details, parallel to V1's function during perception (Bergmann et al., 2016; Kosslyn & Thompson, 2003). A review of studies investigating visual imagery revealed that simulating visual detail with high resolution was the strongest predictor of early visual cortex activity (BA 17 or BA 18; Kosslyn & Thompson, 2003). Furthermore, a recent individual differences study showed that greater visual imagery precision was associated with greater V1 surface area and V1 cortical thickness (but not V2 anatomy; Bergmann et al., 2016). Our findings suggest parallel functionality in the interoception system. The dorsal posterior, granular portion of the insula is considered primary sensory cortex based on pathways of sensory input from the body, analogous to other primary sensory cortices (e.g., V1; Craig, 2002). A within-subject analysis revealed greater activity in this region during highly precise scenario immersion than during the less precise affect focus, both of which occurred in the context of an imagined scenario.

Because this study included a variety of internal bodily sensations in compelling real-world contexts and employed language to evoke fine-grained sensory details, the experimental design provided a strong test of interoceptive simulation. In contrast to the current study, activity in primary interoceptive cortex has not been observed in a handful of studies that examined simulation of physical pain, a sensory experience that involves interoception (Meyer, Williams, & Eisenberger, 2015; Fairhurst, Fairhurst, Berna, & Tracey, 2012; Drabant et al., 2011; Ogino et al., 2007; Koyama, McHaffie, Laurienti, & Coghill, 2005). Pain is a complex subjective experience that often involves distributed activity in the somatosensory and interoceptive systems, as well as other cortical and subcortical systems (e.g., Wager et al., 2013; Hayes & Northoff, 2012; Bingel et al., 2003). The aforementioned studies in which participants simulated pain in imagined or remembered contexts consistently observed neural activity in the somatosensory cortices, providing evidence of tactile simulation (but not interoceptive simulation). Interestingly, in a study in which participants were prompted to relive a physical pain memory, the authors noted that none of the participants reported reexperiencing the pain (i.e., having the experience of being in pain again) and 41% of the participants were unable to report the sensory quality of the pain (Meyer et al., 2015; Morley, 1993). Thus, it appears that activity in primary interoceptive cortex may not have been observed in these studies because it is difficult to simulate the aversive sensory details of physical pain (which is not entirely surprising given that people are typically not motivated to relive or imagine these experiences).

Top–Down Coordination in the Interoceptive System

Accumulating evidence that simulations of sensory experiences are represented in the primary sensory cortices is consistent with emerging views of the brain's large-scale predictive architecture (Barrett, 2017; Chanes & Barrett, 2016; Clark, 2013; Bastos et al., 2012; Lochmann & Deneve, 2011; Friston, 2010). The results presented here support hypotheses derived from a recent account of interoceptive simulation: the EPIC model (Barrett & Simmons, 2015). EPIC provides a new framework for investigating interoceptive functioning in the brain across micro-to-macro scales, including the systems neuroscience that is typical of fMRI studies (for an extension of the EPIC framework, see Barrett, 2017; Chanes & Barrett, 2016; and for other discussions of interoceptive prediction, see Seth & Friston, 2016; Pezzulo et al., 2015; Seth, 2013).

Mental imagery is an ideal fMRI paradigm for investigating top–down prediction and is used extensively to study exteroceptive simulation (Moulton & Kosslyn, 2009). The EPIC framework draws attention to the comparatively little work investigating simulation of internal bodily states. EPIC is based on converging evidence of neural pathways through which top–down simulations impact activity in primary interoceptive cortex and thus represents a departure from traditional bottom–up models of interoception (Barrett, 2017; Chanes & Barrett, 2016; Barrett & Simmons, 2015). Consistent with this account, we observed activity in primary interoceptive cortex and throughout the brainstem during interoceptive simulation initiated by language (in the imagery-based scenario immersion paradigm).

These results complement recent investigations of the distributed, large-scale brain system that emerges in the EPIC framework. Building on advances in the network dynamics of the insular and cingulate cortices (Cauda et al., 2011, 2012; Touroutoglou, Hollenbeck, Dickerson, & Feldman Barrett, 2012; Deen, Pitskel, & Pelphrey, 2011; Seeley et al., 2007), a recent synthesis defined a coordinated, distributed interoceptive/allostatic system, drawing on tract-tracing studies in macaque monkeys and using functional connectivity techniques in humans, and then demonstrated the behavioral relevance of this system (Kleckner et al., 2017). Individuals with increased intrinsic connectivity in this system also displayed increased interoceptive sensitivity, which was measured as the concordance between objective bodily changes during an affective task and subjective reports of corresponding feelings.

The findings reported here, taken together with neuroanatomical and functional connectivity evidence, suggest that EPIC warrants further empirical attention. In this model, simulation occurs during interoceptive functioning generally (not just during immersive imagery). Interoceptive simulation underlies anticipating changes in the body's internal milieu and preparing to meet those needs before they arise (Barrett, 2017; Chanes & Barrett, 2016; Barrett & Simmons, 2015). This allostatic process of achieving stability through change is the most efficient means of keeping the body's many physiological systems in balance (Sterling, 2012; McEwen & Wingfield, 2003; McEwen, 1998; Sterling & Eyer, 1988). The brain coordinates this functioning by anticipating based on prior experiences, initiating top–down simulations that prepare the body for what might happen next, and then adjusting if necessary.[4] In other words, simulation is integral not only to talking about and imagining sensory experiences "offline" but also to constructing "online" experiences unfolding in the world (Wilson-Mendenhall, 2017).

Clinical Implications of Interoceptive Simulation

Our results make a unique contribution to recent discussions of how interoceptive simulation may impact mental health (e.g., Barrett, Quigley, & Hamilton, 2016; Khalsa & Lapidus, 2016; Barrett & Simmons, 2015). Mental imagery is an integral part of exposure and rescripting techniques that are used in clinical settings, especially in treating anxiety and mood disorders (Ji, Heyes, MacLeod, & Holmes, 2016; Pearson et al., 2015). Imagery rescripting, for example, is used to render aversive autobiographical images less unpleasant or emotional (Slofstra, Nauta, Holmes, & Bockting, 2016). Typical instructions are fairly abstract, without a high degree of sensory guidance (e.g., "keep the memory in mind and think of what you could say to yourself that would help or support you in the memory and say that in your memory"). Recent findings suggest that adjusting imagined perceptual features (e.g., colors, object positions) contributes to rescripting (Slofstra et al., 2016). Neuroscience evidence suggests simulation of sensory details in corresponding primary sensory cortices reconstructs the memory (Pearson et al., 2015). This reconstructed experience is then available in memory and can be reinstantiated during future, related situations outside the clinical setting. A novel insight based on findings presented here is that targeting interoceptive sensory details, specifically, could produce an embodied rescripting that contributes to emotional balance in an individual's everyday life.

The importance of vivid sensory details during simulation gains further support from carefully controlled studies of episodic construction, which can be oriented in the past or the future. People who repeatedly imagined consuming a specific food, for example, subsequently consumed less of that food (than those who did not imagine consuming the food, imagined consuming it only a few times, or imagined consuming a different food; Morewedge, Huh, & Vosgerau, 2010). Other empirically demonstrated outcomes of constructing vivid simulations include increasing prosocial intention (Gaesser & Schacter, 2014), reducing implicit racial bias (Lai et al., 2014), and improving problem solving related to worrisome future events (Jing, Madore, & Schacter, 2016). Recent discussions highlight the level of detail as a key dimension through which imagined experiences positively impact well-being (Jing et al., 2016; Schacter, 2012). This view is consistent with neuroscience evidence presented here and elsewhere (e.g., Kosslyn & Thompson, 2003) that the sensory details of simulations guide implementation in primary sensory cortices.

Limitations

No study is without limitations. Our analysis approach included within- and between-subject analyses. Because the between-subject analyses we conducted reflect an archival analysis across two studies, the experimental conditions we examined were not fully randomized. Using two independent data sets allowed us to conduct a strong between-subject test of our hypothesis (in which effects are typically harder to detect). It is possible, however, that differences in the samples, apparatus, or other random factor may have contributed to these effects. The objective measure of interoceptive content, replication of exteroceptive simulation effects in both studies, and the TSNR in insular cortex provide further support for the interpretations presented here. Future research might also consider using functional localizers to precisely map primary interoceptive cortex. This procedure introduces its own challenges, because localizers are more invasive in the interoceptive domain and therefore challenging to implement (including possible unpleasant affective consequences). Because this was an archival analysis, we used coordinates from two independent studies that examined different sources of interoceptive input to localize primary interoceptive cortex.

Conclusion

To our knowledge, these studies provide the first evidence that simulated internal sensations are represented in primary interoceptive cortex. The findings are consistent with emerging models of the brain's predictive architecture, including the interoceptive system. The implication: Words might not break your bones like sticks and stones but they can indeed hurt (or help) you.

APPENDIX A

Scenario Templates for Study 1 and Study 2

Sentence	*Study 1*	*Study 2 (Physical)*	*Study 2 (Social)*
1	State of body and elaboration of activity and/or setting	Setting and activity, and any relevant personal attributes	[Same as physical]
2	Affective event	Setting: visual detail	Setting: auditory detail
3	Affective event: arousal detail using physiological references	Affective event: action	[Same as physical]
4	Affective event: valence detail using pleasant or unpleasant descriptors	Affective event: consequence of the action	[Same as physical]
5	Affective event: categorized the experience with the sentence "You feel a(n) [adjective] [fear, happiness, or sadness]."	Affective event: action in response to consequence	Affective event: another person's action in response to the consequence
6		Affective event: resulting somatosensory experience	Affective event: resulting bodily experience

Study 1 Bodily Details
(Sentence 3 designed to specify arousal)

Affective Event	*Bodily Detail*
Ride rollercoaster	Your heart is pounding and your stomach drops as crisp air blasts your face.
Perform in play	Your heart beats quickly as fresh energy pulses through you.
Jump off seaside cliff	Your stomach is whirling as you flail your arms and legs freely in the air.
Start championship game	You jump in place to shake off the restlessness in your stomach.
Ditch work for road trip	Jumping in your car, you stop for a brief moment to catch your breath.
Slide down water slide	The cool water washes over your tensed abdomen as you slip and slide.
Ski steep hill	Before long you are working up a sweat, sticking to your warm clothing.
Watch TV drama	Settling under the covers, you curl up and wait for the drama to unfold.
Imagine giving speech	You lean back and close your eyes, inhaling a full breath.
Meet significant other's parents	You gently wave as they enter the restaurant and your shoulders naturally settle.
Crush returns gaze	Your crush looks away and you smile to yourself in the private moment.
Make silly bet with friends	You shift to lay your head on a pillow as your friend begins laying out rules.
Notified of award nomination	Giving in to your body's desire to unwind, you relax your muscles, tilting your head back.
Imagine new job night before start	You stretch out and roll over, your body recovering a soothing alignment.
Make impulsive online purchase	Clicking to finalize the purchase, you exhale gradually with a bit of disbelief.
React to car swerving into lane	Your muscles instinctually tighten as you slam your foot on the brakes.
Experience airplane trouble	For a moment all that you sense is a shocking internal numbness.
Witness shooting	You quickly drop behind a car and attempt to control your shallow breathing.
Stuck with broken down car in remote area	Sweating profusely, you try repeatedly to start the exasperatingly unresponsive car.
Realize intruder in house	Launching out of your chair, your heart is palpitating wildly in your chest.

(*continued*)

Affective Event	*Bodily Detail*
Imagine painful medical procedure	As he explains the details, you sense the queasiness in your stomach escalating.
Learn tornado hit family's town	Your stomach cinches in knots as you run outside to call your family.
See snake poised to strike	Gasping, your stomach tightens as you see a snake poised a foot from you.
Wake up late	You remain still, movement disagreeing with your worn out body.
Read disturbing news story	Your body sinks reading that the shooter was a troubled teen who killed himself.
Receive pressing e-mail from boss	Taking a deep breath, you lengthen your spine in an attempt to reenergize.
Learn flu spreading in office	You sense yourself recoil slightly as you click to close out of your e-mail.
Look for table to eat lunch	In the silence, you sense your heart beating steadily as you look around at your peers.
Volunteer to answer hard question in front of others	Scanning the crowd, you hear yourself swallow and linger on the sensation in your throat.
Await midterm grade	You shift in your seat and yawn widely as you rub your eyes.
Win lottery	Your heart is pounding and your legs wobble as you fixate on the string of digits.
Win special prize for submission	Your heart begins pumping and your mouth drops open in shock.
Perform successfully	You bend at the waist into a deep bow and sense your heart thumping rapidly.
Finish running race	You are breathing heavily as your legs rhythmically begin to slow.
Embrace warm family homecoming	You grasp your siblings and parents tightly, inhaling deep into your belly.
Play with family outside	You find yourself quickly out of breath from jumping and laughing.
Run into good friend unexpectedly	You quickly turn around and your body elevates as you are met with a warm smile.
Arrive for holiday with family	Your stomach rumbles gently as the tautness in your chilled body subsides.
Wake up to sweet note	You unfold onto your back and stretch your limbs widely under the sheets.
Take in beautiful nature scene	Your breathing slows and softens as your eyes pour over the expansive vista.
Lounge by the ocean	In this moment, you experience your chest rising and falling softly.
Cuddle with puppy	As her small body relaxes, you sense both your hearts beating evenly.
Read in hammock	As you escape reality, you sense the weight of your body release into the hammock.
Drink cool beverage on hot day	As you yawn widely and deeply, you sense how dry your throat has become.
Float in lake	Your eyes close softly as you center on the warming sensation of the rising sun.
End suffering of pet	A wave of nausea surfaces and you reach out to stabilize yourself.
Win championship with injury	You hear a pop and pant sharply as a throbbing pain erupts in your knee.
Insult abrasive colleague	Your stomach tightens the moment the last sarcastic jab escapes your lips.
Pass big exam but friend did not	You gasp in disbelief of the results and your friend swiftly turns away from you.
Donate blood	Squeezing a ball in your hand, you sense your stomach becoming unsettled.
Receive comfort from friend	You sense your stomach churning as you avert your watering eyes for a second.
Witness near-miss injury of family member	Your heart is racing and your hands feel clammy as you leap off your bike.
Learn sibling moving across country	You gasp loudly, slowing to a fast walk while failing to conceal your dumbfounded state.

(*continued*)

Affective Event	*Bodily Detail*
Finish exhausting workout	A cramping ache in your left quad directs your attention to each small step.
Receive undeserved praise	Peering at your boss, you take a deep breath as you hear him continue on.
Navigate bad weather to see friend	Pulling on your jacket, you shudder slightly as you lift up your hood.
Confess mistake to good friend	As you express your regret, your heartbeat slows to a more natural speed.
Receive good news that cannot share	Wishing you could call him, you close your eyes and release a held breath.
Host costly dinner for friends	As you swipe your credit card, you can hear your heart beating in your chest.
Escape awkward encounter	Saying good bye, your stomach flutters in the wake of the awkward interaction.
Take new job that means leaving best friend	You begin to sweat as you run up the stairs, hearing a faint cheer.
Finish meaningful charity race	Covered in sweat and heart pumping, you pick up your pace.
Reminisce at graduation	Following energetic classmates, you sweat lightly as you march away a graduate.
Celebrate sibling's wedding	You sense your heart pumping as you consciously slow your movements.
Watch finale of favorite show	Clapping your hands together, you gasp in unison with others at the plot twist.
Lose round of playful game	As you jump about gesturing vigorously, you sense your heart beating faster.
Quit job with great co-workers	Walking swiftly to your desk, disheartened coworkers gather around.
Wrap final game with teammates	Smiling as sweat drips off your face, your body is still energized.
Immerse in nostalgic memories	Closing your eyes, you sense the calm rhythm of your heart beating.
Conclude joyful holiday	Your eyes are heavy and begin to close as you exhale easily and softly.
Start new life chapter	You glance at the worn jeans on the floor and spontaneously hold in a breath.
Let go of long, hard day	You sense your stiff neck relax as you rest your head on a pillow.
Miss spouse on fun trip	Anticipating the warm Florida weather, you sense your heart beating softly.
Give as gift something you want	You detect your energy level shift ever so slightly as you hold the package.
Hear song from youth	In the moment following, you allow your eyes to close and release a breath.
Receive school application rejection	Your eyes swell and your body caves inward as hope morphs into devastation.
Miss holiday with family	Your body quivers and you fight back tears when the airport is officially closed.
Hit dog with car	Tears begin to swell as you leap out of the car as fast as you can.
Learn significant other cheating	Your stomach is nauseated, the shocking infidelity settling into your body.
Face credit card debt	Your stomach becomes uneasy as you examine the accruing charges.
Learn cancer has returned	You bury your head in your hands, inhaling in short sharp breaths.
Search for missing family member	Your throat instantly goes dry when you think of the danger she might be facing.
Watch starving children ad	As the commercial ends, you close your eyes and sense yourself exhale.
Miss out on movie tickets	Your body sinks as you scan the other lackluster possibilities on the board.
Think about those less fortunate	His presence remains with you as your muscles unwind and loosen.
Wait for dinner when hungry	Your stomach grumbles as you turn to relay the message to your friends.
Realize new recipe not very good	Setting down your fork momentarily, you hear your stomach quietly rumbling.
Fail to fix technical problem	After another failed attempt, you slowly close your computer and let go of a breath.
Discover pimple on face	You stare at your face, motionless until a sigh escapes and your shoulders sink.
Find photo of deceased grandparent	You softly close your eyes, briefly tearing up as you hold the photograph.

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Notes

1. Supplementary material for this paper can be retrieved from https://www.affective-science.org/data/sup/SupFigure5.tiff and https://www.affective-science.org/data/sup/SupFigure6.tiff.
2. We confirmed in further analyses that the results were consistent across both Study 2 scenario immersion conditions. Study 1 scenario immersion showed significantly greater activity than Study 2 scenario immersion involving social evaluation and Study 2 scenario immersion involving physical danger (all tests $p \leq .001$, significant correcting for multiple comparisons).
3. Given the moderate skew in this ROI, we computed the equivalent nonparametric test for each contrast, which showed consistent results: (3a) significant difference observed in one-sample Wilcoxon signed rank test ($W = 136, p < .001$); (3b) significant difference observed in a Wilcoxon signed ranks test ($z = -2.66, p = .008$); (3c) significant difference observed in a Mann–Whitney test ($U = 10.5, z = -4.76, p < .001$).
4. For neuroanatomical and circuitry details, see Kleckner et al. (2017), Chanes and Barrett (2016), and Barrett and Simmons (2015).

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