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Research report

Error blindness and motivational significance: Shifts in networks centering on anterior insula co-vary with error awareness and pupil dilation

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ABSTRACT

This investigation aims to further our understanding of the brain mechanisms underlying the awareness of one's erroneous actions. While all errors are registered as such in the rostral cingulate zone, errors enter awareness only when the anterior insula cortex is activated. Aware but not unaware errors elicit autonomic nervous system reactivity. Our aim is to investigate the hypothesis that activation in the insula during error awareness is related to autonomic arousal and to inter-regional interactions with other areas of the brain. To examine the role of the anterior insula in error awareness, we assessed its functional connectivity to other brain regions along with autonomic nervous system reactivity in young healthy participants who underwent simultaneous pupil-diameter and functional magnetic resonance imaging measurements while performing a complex and error-prone task. Error blindness was associated with failures to engage sufficient autonomic reactivity. During aware errors increased pupil-diameter along with increased task-related activation within, and increased connectivity between anterior insula and task-related networks suggested an increased capacity for action-control information transfer. Increased pupil-diameter during aware errors was furthermore associated with decreased activation of the default-mode network along with decreased insular connectivity with regions of the default mode system, possibly reflecting decreased task-irrelevant information processing. This shifting mechanism may be relevant to a better understanding of how the brain and the autonomic nervous system interact to enable efficient adaptive behavior during cognitive challenge

1. Introduction[1]

Here we seek to understand the brain- and autonomic mechanisms underlying the awareness of one's erroneous actions. The relevance of insight into the conditions under which error awareness arises is probably most readily apparent in pathologic conditions that are associated with deficits in error awareness. Deficits in error awareness occur in health as well as in pathology. Impaired error processing abilities have for instance been suggested to mediate poor insight in one's deficits after traumatic brain injury [33,51]. This represents a key obstacle to rehabilitation, and is a significant predictor for overall long-term outcome, return to community living, and productive lifestyle (see for a review [42]).

The recent literature in the field of error awareness can be characterized by an increasing attempt to explore mechanisms and conditions under which error awareness occurs. The anterior insula cortex has been found to activate selectively to aware errors, whereas the rostral cingulate zone shows no difference between unaware and aware errors [34,41]. However, during error awareness, the insula's variety of operating characteristics within several contexts, such as autonomic processes [15,16], interoception [10], visceral sensory and motor processes, limbic integration [3], and large-scale brain network shifts [45,60,62], has yet prevented a clear distinction of its precise functional contributions to error awareness. Limited data is available on the networks of the human insula cortex, and reports on arousal signals mediating insula networks are largely lacking.

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[1] This study capitalizes on analyses of pupil diameter, which as a result of advancing insights were largely conceived only after data collection. Since these analyses are used to test hypotheses that were not part of our original set of predictions and analysis plans, we wish to emphasize the exploratory nature of the present results.

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By articulating the insula's functional network and autonomic function, we aim to gain more insight into the nature of the insula's activity during error awareness. This approach was specifically motivated by the observation that the insula cortex plays a principal role in error awareness, in the mapping of autonomic and visceral functions [12], and is involved in neural networks dedicated to the evaluation of motivational salience [60,62]. Moreover, several studies place increasing emphasis on the changes in the autonomic nervous system during error awareness (e.g., [50,71]). Traditionally, the use of terms like vegetative or involuntary to describe the function of the autonomic nervous system implied that the autonomic nervous system has little to do with cognitive or voluntary actions. However, studies of autonomic activity that accompanies attention, cognitive effort, and the orienting to surprising events, have demonstrated that the autonomic nervous system is not simply a 'non-cognitive' part of brain function [35]. Autonomic arousal is commonly thought to prepare the organism to respond to changed internal and external requirements, by recruiting the necessary mental as well as physical effort [57,68].

One index of autonomic arousal is pupil dilation. Pupil diameter constitutes an indirect index for the tonic and phasic modes of locus coeruleus-norepinephrine (LC/NE) function [56], that can be linked to lapses of task engagement and poorer performance [29]. In monkeys, the firing of LC/NE neurons is followed immediately by pupil dilation [37], in particular in relation to the energization of behavior [69]. Within cognitive tasks, baseline pupil diameter (just preceding a task-relevant stimulus) and evoked pupil dilation (following the stimulus) can serve as indices for tonic and phasic modes of LC/NE function, respectively [1,47]. While small baseline pupil diameter and large task-evoked dilations have been proposed to correspond to effortful task engagement, task *dis*engagement has been associated with large baseline diameter and small task-evoked dilations [29]. In line with these findings, pupil dilation has been shown to increase after aware errors, but not after unaware errors [71]. These findings on LC/NE function and pupil dilation emphasize the link between autonomic function and cognition.

In recent years, researchers have begun to investigate the link between brain function and autonomic function during cognitive operations. Although intriguing, thus far these new studies leave open the question to what extent autonomic signals during cognitive operations are related to brain function during error awareness, and to inter-regional brain network communication.

Here, in order to capture the relation between error awareness, autonomic activity and neural network activation and connectivity, participants performed an antisaccade task, known to yield both aware and unaware errors [25,41,49], while undergoing simultaneous fMRI, oculomotor and pupil diameter measurements. We quantify anterior insula's functional activation and functional connectivity and its relation to changes in pupil diameter one second before error awareness. The aim is to investigate the hypothesis that activation in the insula during error awareness is related to autonomic arousal and to inter-regional interactions with other areas of the brain. We examine moreover if these inter-regional interactions of the insula cortex during error awareness are mediated by autonomic arousal. We hypothesized that pupillary responses before error awareness are related to activity in the anterior insula and its related functional networks. Although such a link cannot disentangle whether the pupil response and the anterior insula networks serve as precursors or as sequelae to awareness of an error, such a link would yield evidence that a crucial function of the anterior insula is to integrate homeostatic regulation and neural network functions once an error has been detected.

2. Material and methods

2.1. Participants

23 healthy right-handed volunteers (17 females, mean age 21,5 ± 2,0) with normal or corrected-to-normal vision participated in the experiment after giving written informed consent according to the Helsinki Declaration. They were paid 50 Euros for participation. None of the participants had a history of neurological or psychiatric disorders or eye problems, and none were taking medication influencing the central nervous system or cardiovascular systems. Participants were selected beforehand in a task-session outside the scanner. Selection was based on a minimum of 15 errors in the aware/unaware condition with a false alarm rate lower than the aware/unaware error rates and based on a post-experimental self-rating of uncertainty in performance evaluation (maximum 5% on an analogue scale 1–100%). The aim of the uncertainty rating was to assess participants' subjective feeling about their response evaluation in order to explore how well they could assess their own eye-movements beyond guessing. The questionnaire explored the level of uncertainty experienced in evaluation (correct versus incorrect) of their antisaccadic-response on an analogue scale (0–100). None of the participants reported doubts higher than 5%. Two participants were excluded due to motion-correction estimates above 2 mm and anatomical deviations evident after medical inspection of structural scans. Insufficient number of errors for fMRI analysis led to exclusion of a third subject.

2.2. Task

We examined unaware and aware errors in an antisaccade task commonly used to study error awareness [25,41,49]. Participants were instructed to fixate on a central target and generate an immediate eye movement away from an abrupt peripheral target to its mirror location on the opposite side of the screen without making an eye movement to the peripheral target itself. The temporal order of stimulus presentation is displayed in Fig. 1a. The trial started with a central fixation dot surrounded by two square outlines (each subtending 3.8° of visual angle; distance from fixation 12.4°; display duration 1000 ms). After a 150–300 ms jittered fixation gap, the peripheral target (a white circle subtending 2.9°) was presented for 117 ms in the left or the right square. To induce erroneous responses a precue was presented in 50% of the trials [41,49] briefly (50 ms) thickening the outlines of the square at the opposite side of the target and validly indicating the target location. After a response window of 880 ms, a cross appeared for 500 ms in the correct square, indicating the correct gaze direction.

Immediately after each eye-response and after the correct gaze direction had been indicated by the cross in the correct square, participants were to evaluate their performance (within 1500 ms) by pressing one of two buttons. They had been instructed that each initial eye movement towards the peripheral target was classified as an error even when they ended up moving their eyes in the correct direction. With the button press they were to indicate whether their antisaccadic response was correct (no initial eye movement toward the target) or incorrect (an initial eye movement toward the target). Previous error awareness tasks employed a motor response only upon error detection. In the present paradigm, participants press a button on each trial (the left/right button, randomized across participants) during the evaluation to assess their antisaccadic response. Thus participants press a button during aware and during unaware errors; hence, the motor response is kept equal across error-types. The erroneous responses that participants had rated as incorrect were classified as aware errors, and erroneous responses rated as correct were classified as unaware errors. If the erroneous eye movement was redirected to the correct (opposite) side of the screen, the response was labeled "corrected error".

On trial numbers 20, 40, 60 and 80, an instruction screen (duration: 2 s) appeared, reminding participants to keep saccading at fast pace. A black screen with jittered duration (16, 500, 1000, 1500 ms) was displayed between trials, and 10% of the trials were 'null events' (fixation-only trials of 5952 ms). Participants completed 3 blocks of 100 antisaccade trials, each lasting 11 min. For assessment of the pupil response, light flux was calibrated to equal luminance across trials with

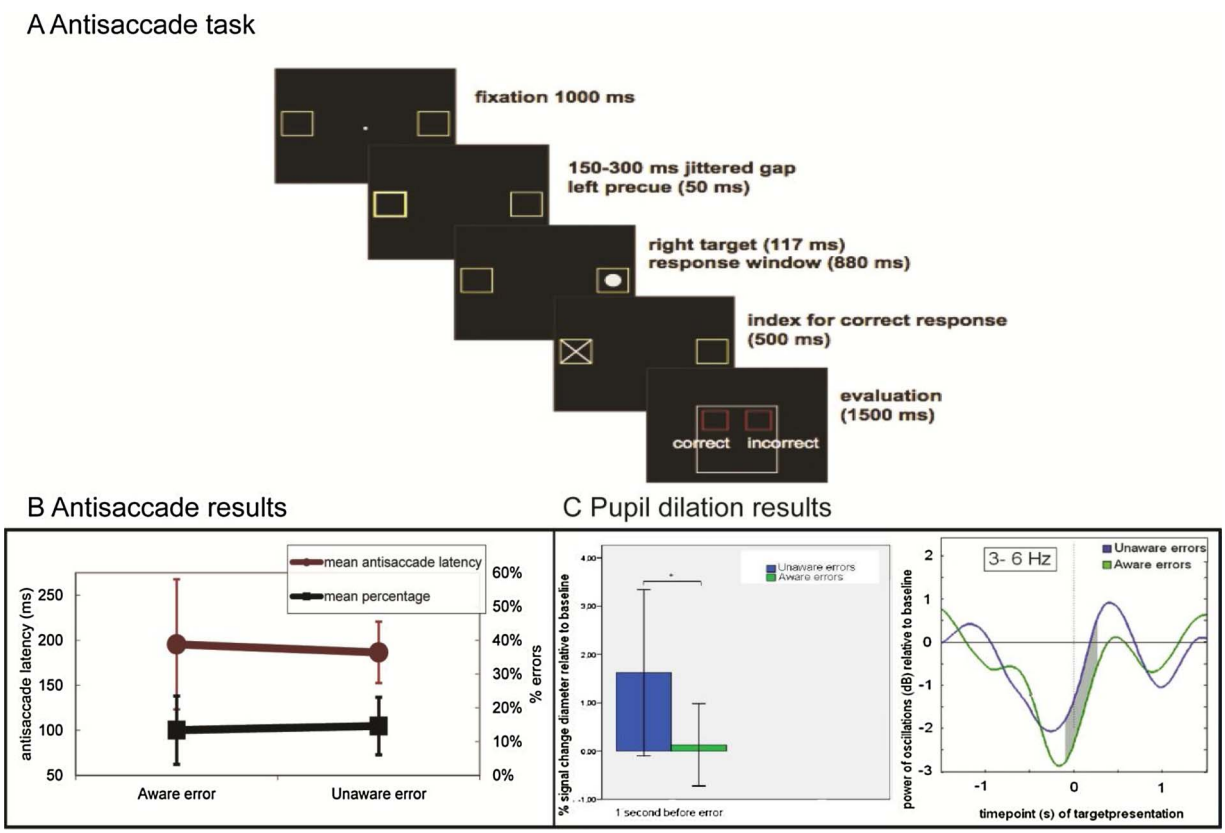

Fig. 1. A. Antisaccade task: Participants were instructed to fixate on a central target and generate an immediate eye movement away from an abrupt peripheral target to its mirror location on the opposite side of the screen (correct response) without making an initial eye movement to the peripheral target itself (incorrect response). After the participant made an eye movement, a cross appeared in the correct square, indicating the correct gaze direction. Subsequently, they were to evaluate their performance (correct/incorrect) by pressing one of two buttons. The erroneous responses participants had rated as incorrect were classified as aware errors and erroneous responses rated as correct were classified as unaware errors. **B.** Antisaccade results: Aware errors and unaware errors occurred equally often and were similar in mean latency. **C.** Pupil dilation results: Signs of autonomic reactivity in pupil diameter vary with awareness. **C. left panel:** Mean (± SE) pupil diameter in the 1-s period before errors, plotted relative to baseline (mean dilation across the whole task) across all subjects (N = 23). The significance asterisk denotes that the pupil diameter was significantly larger before unaware (1.6 ± 4.1%) compared to aware errors (0.2 ± 2.0%; t(22) = 1.71; $p < 0.05$.). **C.right panel:** Power of low-frequency oscillations (3–6 Hz) for a period of 4 s around peripheral target presentation, plotted relative to baseline across all subjects. Gray regions reflect time windows with significantly higher power in low frequency pupillary oscillations on unaware errors than on aware errors. Oscillatory power between unaware and aware errors was considered significantly different when at least 156 contiguous ms (40 time points) survived a paired-samples *t*-test at $p < 0.05$. A stable decrease in low-frequency oscillations during the visual appearance of the fixation point in both aware and unaware errors reflects increased vigilance caused by the fixation point. The decrease in low-frequency oscillations with aware errors was greater than with unaware errors, suggesting greater autonomic disengagement from the task during unaware errors.

the program Colorfacts 7 and the color calibration system "EyeOneMonitor" (www.datacolor.eu) and tested for equal pupil luminance response across precue conditions. There was no significant difference in pupil dilation between trials with (0.4 ± 1.1) and without precue (0.4 ± 1.2; t(22) = 0.01, $p < 0.995$).

Light in the scanning environment was constrained to video presentation of stimuli against a black background. The projecting screen for the stimuli was placed in front of the window to the adjacent scan-operator room, such that the window was not visible for the participant. The adjacent scan-operating room, was lighted with constant, non-varying ambient light, as pupil size is sensitive to change in ambient light flux.

2.3. Behavioral data acquisition and analysis

Oculomotor, pupil and button-press responses were recorded with 2 interconnected PCs: An eye-tracker PC (ViewPoint EyeTracker, Arrington Research) and a presentation PC (Neurobehavioral Systems, www.neurobs.com, Albany, USA). Both PCs were connected to the MRI-scanner allowing for the time locking of stimuli, responses and fMRI image acquisition. The participant's left eye was continuously monitored with an MRI-compatible infrared oculographic limbus tracker (Resonance Technology, Inc.) attached to the head coil and placed 3 cm beneath the participant's left eye. The eye-tracker registered eye movements, aspect ratio and diameter of the pupil with a sampling rate of 60 Hz along with scanner pulses and stimulus onsets. Before the scan, a 9-point calibration was performed and calibrated eye position was slip corrected during the task to eliminate slow drifts. Calibration and stimuli were presented on a 66 cm x 88 cm screen, placed at a 4-m viewing distance at the front end of the scanner and seen through a mirror above the participants' heads.

Saccade onsets, amplitudes and directions were detected with in-house Java-based software using minimum amplitude (> 1.5°) and velocity (> 30°/s) criteria and were subsequently double-checked by 2 raters. In line with common definitions [26] we excluded trials in which subjects initiated saccades faster than 80 ms after target appearance (3.3 ± 4.1% (s.d.) of all trials), trials in which subjects were looking away from fixation during target presentation (2.7 ± 3.9%), blinked during target appearance (0.6 ± 1.2%) and trials for which the eye-movement data were not interpretable due to poor quality of the eye-tracker signal (5,0 ± 4.3%).

To compute pupil diameter, data were cleaned using Matlab algorithms. Artifacts, including blinks, were defined as points greater than 2 standard deviations above or below the mean, occurring too rapidly to signify dilation. These points were replaced using spline interpolation from the preceding and following points. Next, the data were converted to percent signal change from the entire time series mean. This was done to facilitate cross-subject (i.e., different pupil sizes across subjects)

and cross-condition comparisons, without the need to normalize using a pre-stimulus baseline correction. Normalizing with the overall mean of pupil diameter was done to exclude the effect of variation in pupil size across subjects. Note that normalizing based on the pre-trial resp. or inter-trial window was not possible as this was the window of interest. Hence, pupil diameter results, as illustrated in Fig. 1a, are given in % signal change relative to the mean pupil diameter across the entire task, based on the continuous (pre-epoched) time series (excluding artifacts), and are presented for a period of 1 s before the presentation of the peripheral target. The pupil metric is thus baselined not to a pre-target baseline, but to the mean pupil diameter during the entire task. Our baseline should therefore not be sensitive to the amount of total variance, nor to how that variance is structured in time. The choice for the 1 s pre-error window was partly based on the previous observation in antisaccade tasks that "measurements of pupil dilation will almost automatically be influenced by the pupillary light reaction: Because the imperative stimulus consists of a white circular expanse, the luminatory properties of the visual field change once the stimulus sets in. Additionally (and more severely), the type of the trial might systematically influence the size of the pupillary light reflex, because on error trials, the subjects initially move their gaze toward the light stimulus at first, whereas on correct trials, this is not the case" [71], p.3025). The pre-error window (which, for the average error RT, would span approximately −0.8 to +0.2 s around target onset) will appropriately capture a pure baseline period – even the relatively fast light reflex will not have kicked in by 0.2 s post-target. Wessel et al. (Fig. 5in [71]) show that confounds relating to saccades take a similarly long time to onset.

To test for statistically significant differences in pupil diameter between aware and unaware errors a paired-samples *t*-test was computed. For individual-difference covariation analyses, pupil data in a period of 1 s before the presentation of the peripheral target on error trials were aligned to each event of interest, averaged across the time window and trials to produce an average pupil diameter percent signal change value for each participant for each of the two trials types: aware and unaware errors. Power of low-frequency oscillations of pupil diameter (3-6 Hz) was computed by convolving the single-trial pupil diameter of cleaned pupil data with a family of Morlet wavelets. Slow pupillary oscillations are a characteristic of decreasing subjective alertness due to unstable fluctuations in central sympathetic activity [72]. A paired-samples *t*-test was computed to test for statistically significant differences in the power of low-frequency oscillations between aware and unaware errors. Pupil oscillation results, as illustrated in Fig. 1b, are given in dB for a period of 4 s around peripheral target presentation (−2 to +2 s) with grey areas indicating significant differences at p = 0.05. Oscillatory power was considered significantly different when at least 156 contiguous ms (40 time points) survived a paired-samples *t*-test at $p < 0.05$. The window size was initially based on requiring at least one full cycle of activity at 6 Hz (technically 6.4 Hz to account for some spectral smoothing).

2.4. fMRI acquisition, GLM and functional connectivity

Acquisition. Functional images were acquired on a Philips 3T MRI system equipped with echo planar imaging (EPI) capabilities using a standard head coil for radio frequency transmission and signal reception. Functional scans of the entire brain were acquired with a single-shot, gradient-recalled EPI sequence parallel to the AC–PC plane (TE/TR = 28/2000 msec; 30 axial slices; slice thickness 3 mm; inter-slice gap 0.3 mm; voxel size 3 × 3 x 3 mm; FOV = 222 × 2 mm; 96 × 96 in-plane resolution/matrix size, 90° flip-angle). The first 2 volumes were discarded to allow for T1 equilibration effects. The duration of the antisaccade task was three times 11 min (335 scans per scanblok). High-resolution anatomical images were subsequently acquired using a 3-D T1-weighted scan in steady state sequence (TE/TR = 4.6/9.69 ms; 182 sagittal slices; slice thickness1.2, inter-slice gap 0.3 mm; voxel size 1 × 1 × 1 mm cubic; FOV = 25 × 2 cm; 256 × 2 in-plane resolution, 8 ° flip angle, sagittal orientation).

2.5. Preprocessing and GLM

Preprocessing of the functional data and calculation of the contrast images for statistical analysis was done with FEAT (FMRI Expert Analysis Tool) Version 5.63, a part of FSL (FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl). Functional images were realigned to compensate for small head movements, slice-time corrected, spatially smoothed with a 5-mm full-width half-maximum Gaussian kernel, filtered in the temporal domain using a high-pass filter with a cutoff frequency of 1/50 Hz to correct for baseline drifts in the signal and prewhitened [74]. For each experimental run of each participant, the overall activity, as evoked at the timepoint of the peripheral target-presentation, and separately for correct responses and error commission was modeled (2 levels: aware errors vs. unaware errors) and each regressor was convolved by a prototypical synthetic hemodynamic response function and its first derivative. To remove any artefactual signal changes due to head motion, six parameters describing the head-movements (three translations, three rotations) were included as confounds in the model. In the second-stage analysis participants were treated as a fixed factor to concatenate the three experimental runs. Contrasts pertaining to the main effects constituted the data for the third-stage (mixed effect) analysis, where the significance of observations was determined across the group of 23 subjects using FLAME 1 and 2 (FMRIB's Local Analysis of Mixed Effects, [61]. For each whole brain comparison of aware versus unaware trials, a cluster-corrected threshold of $p < 0.001$ corrected for whole-brain multiple comparisons was set using Gaussian random field theory (GRFT).

The presence of the pre-cue was not integrated in the GLM model for three reasons. First, there was no significant difference between the occurrence of aware or unaware errors on precue trials. Second, there was no significant difference in pupil dilation between trials with (0.4 +/− 1.1) and without precue (0.4 +/− 1.2; $t(22) = 0.01$, $p < 0.995$). Would that have been the case, then it could have been a potential confound in the contrast correct vs error trials, but this was not the case. Third, the goal of the precue was to induce errors to have an sufficiently high amount of error trials for analyses. We strived for a minimum of 15 errors in the aware/unaware condition. A split in with/without precue conditions would have yielded too few trials per condition for the analyses. The behavioral saccadic results did yield the expected strong effects on correct vs error trials (more errors on precue trials than on correct trials) and (also as anticipated) no behavioral effects of precues on aware vs unaware errors.

In subsequent whole brain covariance analysis with individual pupil diameter values we report cortical regions with a threshold of $p < 0.05$ cluster-corrected for whole-brain multiple comparisons (using GRFT).

2.6. Functional connectivity

For functional connectivity analysis, the psycho-physiological interaction (PPI) method was applied. We following the procedures for PPI analysis that is standard and widely used in SPM and several other packages [28]. PPI makes inferences about regionally specific responses co-varying with the interaction between the psychological factor and the physiological activity in a specified seed area. Bilateral anterior insula represented an a priori region of interest as error awareness seems to place particularly strong demands on bilateral anterior insula [41]. The seed anterior insula subtended the three principal short insular gyri (anterior, middle, posterior) and the accessory and transverse insular gyri, all anterior to the insular sulcus. Definition was based on the MNI structural atlas of the FSL-atlas toolbox and literature on neurosurgical landmarks [23,44]; Ture, Yasargil, Al-Mefty, Yasargil, 1999). There were two < BOLD time series > X < task condition > vectors, one for aware errors and one for unaware errors. These two IVs

were created from the AIC time series by multiplying with zeros and ones. The entire time course of activity in bilateral anterior insula cortex (AIC) seeds was extracted for each subject and activity during 6 TRs following each aware and unaware error was used as an independent variable in a GLM. AIC time course was multiplied with a condition vector that was ones for 6 TRs following the error, and zeros otherwise. These resulting vectors were then used as regressors, in a separate regression, which included the aware and unaware vectors as the independent variables of interest. The dependent variable was the BOLD time series at each other voxel in the brain. The direct comparison of beta coefficients between these two conditions indicates statistically significant modulations in connectivity with AIC as a function of error awareness. For each individual, this procedure yielded a functional connectivity map identifying areas where BOLD signal changes were temporally coupled with signal changes derived from bilateral AIC seeds as induced by aware as compared to unaware errors. The three experimental runs were concatenated and third level group analyses were conducted with a cluster-corrected statistical threshold of $z < 2.3$ and $p < 0.05$, correcting for whole-brain multiple comparisons.

2.7. Individual differences covariance analysis

To investigate the relationship between the neural response during aware versus unaware errors on the one hand and the pupil response on the other, we computed the pupil dilation value for aware errors as compared to a baseline pupil value across the whole task for each individual. In brief, this analysis focuses on how inter-individual differences in pupil responses during aware errors correlate with brain activity and connectivity for the contrast aware > unaware. The aim of the baseline comparison for the pupil in our analyses was a correction for differences in baseline pupil size across participants. Thus no aware-unaware subtraction took place in the pupil data; only a baseline comparison (see also discussion).

The resulting individual pupil values during aware errors were baseline-subtracted, so that the result becomes independent of the baseline. These demeaned aware error-related pupil values for each participant were incorporated as a covariate in a GLM regression model (fitted response to aware error vs no unaware error with the fMRI regressor on target appearance) and all voxels exceeding the cluster-corrected threshold of 0.05 in the mean *z*-map were determined. Thus, apart from explaining changes in functional activation on the basis of the target cue (during aware −unaware errors) alone, it was assessed which neural changes during the display of the target cue (during aware-unware errors) co-varied with the variation in the pupil in the 1 s window before aware errors (as compared to the whole-task pupil baseline).

The same demeaned pupil diameter values were subsequently entered as covariates into a PPI analysis and all parameter estimates at each voxels exceeding the cluster-corrected threshold of 0.05 ($z = 2.3$) in the mean z-map were determined. Thus, apart from explaining changes in functional connectivity on the basis of the error class alone, it was assessed whether changes in functional connectivity during aware versus unaware errors can be predicted by individual differences in pupil diameter in the1 s window before aware errors.

3. Results

3.1. Behavioral results

The mean error rate was 28.1 ± 13.7% (s.d.), and the majority of errors were made on trials with a precue (80.2 ± 15.0%). Pair-wise comparisons indicated that aware errors and unaware errors occurred equally often (13.5 ± 10.4% vs. 14.6 ± 8.7%; $t(22) = 0.43$; $p = 0.67$; see Fig. 1b), and there was no significant difference between the occurrence of aware or unaware errors on precue trials (81.9 ± 17.1% vs 73.5 ± 23.6%; $t(22) = 1.53$; $p = 0.14$). Unaware errors were corrected significantly more often than were aware errors (94.2 ± 14.9% vs. 66.3 ± 31.3%; $t(22) = 3.9$; $p < 0.001$). False alarm rates below 5.1% indicated that participants rarely reported an error when they made a correct antisaccade.

Erroneous responses were initiated faster than correct responses (191 ms vs. 284 ms; $t(22) = 10.3$; $p < 0.001$). Unaware and aware errors were similar in mean latency (186 ms vs. 195 ms; $t(22) = 0.71$; $p = 0.49$; see Fig. 1b). There was no significant post-error slowing, as indicated by a nonsignificant difference between onset latencies on trial following corrects versus those following errors (263 ms vs. 255 ms; $t(22) = 0.17$; $p = 0.10$). Post-error onset latency was also not different following aware versus unaware errors (255 ms vs. 254 ms; $t(22) = 0.13$; $p = 0.899$).

There was no significant difference in pupil dilation between trials with (0.4 ± 1.1% signal change) and without precue (0.4 ± 1.2% signal change, $t(22) = 0.007$, $p = 0.99$), suggesting that precue luminance did not influence our results.

3.2. Pupil diameter: signs of autonomic task engagement on aware errors and disengagement on unaware errors

Effortful processing and engagement is associated with intermediate pre-stimulus pupil diameter and large stimulus-evoked dilations; conversely, task disengagement is associated with large pre-stimulus dilated pupil diameter and a small stimulus-evoked pupil response [29]. To test the hypothesis that unaware errors are associated with autonomic signs of task disengagement and that aware errors are associated with autonomic signs of effortful processing, we examined pupil diameter immediately before and after aware errors. Results are given in% signal change, relative to mean pupil diameter across the entire time series.

Consistent with previous results [71] pupil diameter was significantly larger before unaware (1.6 ± 4.1%) compared to aware errors (0.2 ± 2.0%; $t(22) = 1.71$; $p < 0.05$). Pupil size did not change after unaware errors (1.5 ± 3.9%), but increased significantly following aware errors (0.8 ± 2.3%; $t(22) = 1.79$; $p < 0.04$; Fig. 1c).

Low-frequency fluctuations in pupil diameter index autonomic dysregulation during decreases in self/reported vigilance [72,73]. To examine pupil diameter responses for signs of autonomic dysregulation during unaware errors we computed the power of low frequency oscillations (3–6 Hz) of pupil diameter in a period of 2 s before and 2 s after unaware- and aware errors relative to mean pupil diameter across the entire timeseries (baseline). Oscillatory power between unaware and aware errors was considered significantly different when at least 156 contiguous ms (40 time points) survived a paired-samples *t*-test at $p < 0.05$. Significantly stronger power in slow oscillations were observed preceding and following unaware errors compared to aware errors. Gray regions Fig. 1c reflect time windows with significantly higher power in low frequency pupillary oscillations on unaware errors than on aware errors (Fig. 1c).

3.3. Aware versus unaware errors: fMRI activation and functional connectivity

Consistent with a host of previous findings, we observed that the rostral cingulate zone (RCZ) was more active during errors (especially during aware errors) than during correct responses (for review, see [59]. Here, we chose to focus on the aware versus unaware contrast. Aware compared to unaware errors yielded significantly increased activation in right anterior insula, bilateral somatosensory cortex, thalamus, areas in the anterior cingulate, frontal eye fields and intraparietal sulcus (Fig. 2a and Supplementary Table 1). PPI analyses showed increased functional connectivity of the anterior insula with bilateral somatosensory cortex and bilateral intraparietal sulcus (Fig. 2b and Supplementary Table 2).

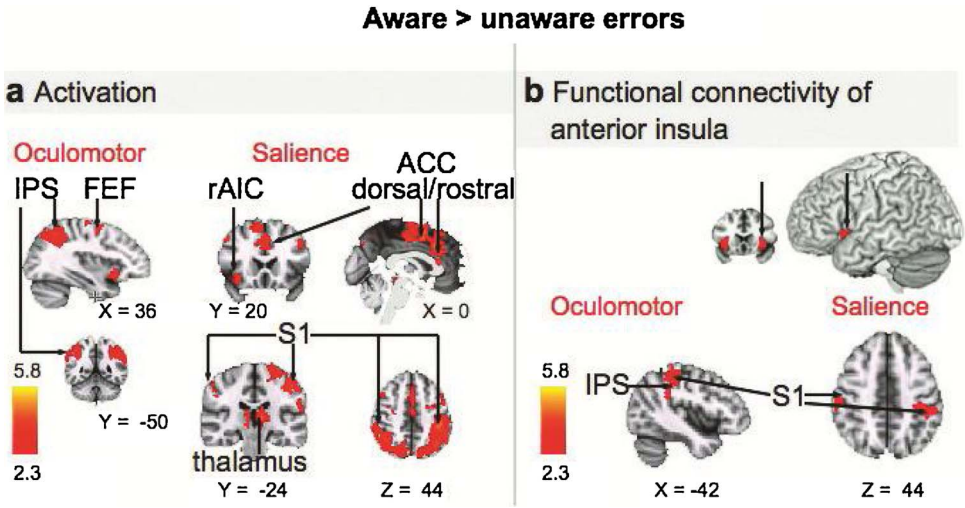

Fig. 2. BOLD activation and functional connectivity of anterior insula for aware errors. **(a)** Statistical parametrical map of difference in BOLD activation between aware and unaware errors. Red and yellow voxels represent clusters of significant BOLD signal increase. **(b)** Statistical parametrical map of difference in functional connectivity of anterior insula cortex between aware and unaware errors. Red and yellow voxels represent clusters of significant BOLD signal correlation between the seed region anterior insula cortex and all other voxels in the brain during aware errors as compared to unaware errors. For a full list of activated regions (z = 2.3, whole-brain cluster-corrected, p = 0.05), see Supplementary Table 1 and Table 2. Note: L/R = left/right, IPS = intraparietal sulcus, FEF = frontal eye fields, AIC = anterior insula cortex, ACC = anterior cingulate cortex, S1 = somatosensory cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. Pupil diameter predicts shifts in engagement between default mode and task-focused brain networks

To link the BOLD response to the pupil response, we correlated functional activation (aware > unaware) across subjects with % signal change in pupil diameter in the 1-s period before errors. Pre-aware error pupil diameter correlated with activation in the right anterior insula, dorsal anterior cingulate, right somatosensory cortex and in oculomotor task control structures (frontal eye fields, intraparietal sulcus). Negative correlations with pre-error pupil diameter were observed in structures associated with the default mode network, including anterior medial prefrontal cortex, frontal pole, precuneus and posterior cingulate (Fig. 3 and Table 1).

To link functional connectivity of the anterior insula to pupil diameter, we correlated individual differences in the anterior insula-seeded PPI with % signal change in pupil diameter in the 1-s period before errors. Here we found positive correlations (i.e., larger pupil diameter predicts stronger insula-seeded functional connectivity) in oculomotor control structures including intraparietal sulcus and left parietal-occipital junction, and somatosensory cortex. Negative correlations (larger pupil diameter predicts weaker insula-seeded functional connectivity) were observed in default mode network regions, including anterior medial prefrontal cortex and frontal pole (Fig. 4 and Table 2).

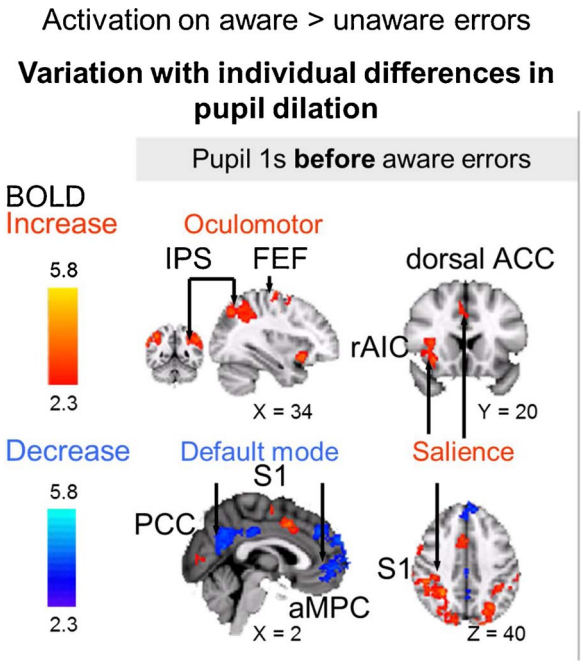

Fig. 3. Links between BOLD activation and pupil diameter for aware errors. Increased activation in the task control structures and decreased activation in the default-mode network are predicted by pupil diameter immediately before aware errors. Statistical maps of the correlation between individual differences in pupil diameter and corresponding BOLD contrast (aware > unaware errors). The spatial distribution of correlation coefficients shows both positive correlations (red and yellow voxels) and negative correlations (blue voxels) at cluster-corrected statistical thresholds of z = 2.3, p = 0.05. For a full list of activated regions, see Table 1. Note: L/R = left/right, IPS = intraparietal sulcus, FEF = frontal eye fields, AIC = anterior insula cortex, ACC = anterior cingulate cortex, S1 = somatosensory cortex, PCC = posterior cingulate cortex, aMPC = anterior medial prefrontal cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

The goal of the current study was to capture the relationship between states of error awareness and patterns of activation and connectivity in neural networks centering on the anterior insula in relation to autonomic activity while participants performed the antisaccade task. To date, pupil diameter changes during cognitive control tasks have scarcely been addressed in studies of functional brain connectivity (for a recent example see [24]. Therefore, for a thorough understanding of the relation between the pupil-diameter patterns during error awareness and error blindness, and the associated changes in the insula cortex and its related networks, we will start the discussion with an interpretation of the observed pupil dilation pattern.

4.1. Pupil diameter findings

We found that a change in awareness state involved concomitant changes in autonomic activity as indexed by changes in pupil diameter. Pupil diameter was significantly larger before unaware compared to aware errors.

Within cognitive tasks, baseline pupil diameter (preceding a task-relevant stimulus) and evoked pupil dilation (following the stimulus) can serve as indices for tonic and phasic modes of LC/NE function, respectively [2,48,56]. The notion that within participants, pupil size is larger before unaware errors than aware errors; but between participants, larger pre-error pupils correspond to greater engagement of task-relevant brain regions and less engagement of the default mode network, may seem paradoxical. Yet it is in line with the theoretical interpretation of the physiological characteristics of the pupil response based on the adaptive gain theory [1], which states that task engagement is modulated by tonic LC activity in a way that mirrors the classic

Table 1
Brain regions in which the aware > unaware error contrast co-varied with pupil diameter (cluster corrected at z = 2.3, p = 0.05).

(a) BOLD effect varying with pupil diameter before aware errors				
Brain region	X	Y	Z	Max z
Positive covariance				
R AIC	30	22	−4	4.10
R MIC	40	2	−4	3.31
R S1	48	−26	50	3.26
R dorsal ACC	6	6	42	4.09
L dorsal ACC	−2	12	38	3.24
R suppl.motor cortex	6	−6	62	3.27
R IFG	56	10	4	4.06
R FEF	34	−8	56	4.05
R IPS	56	−36	34	4.07
L IPS	−40	−44	−34	3.40
L parietal occipital junct.	−26	−62	36	3.37
R V2	14	−66	−6	3.36
Negative covariance				
R aMPC	10	50	−16	3.38
L aMPC	−8	50	−16	3.39
R frontal pole	12	48	−16	3.41
L frontal pole	−10	54	−18	3.37
R PCC	2	−26	36	3.29
R precuneus	8	−56	22	3.39
L precuneus	−8	−56	26	3.35

Coordinates are given in MNI space.
Note. L/R = left/right, AIC = anterior insula cortex, MIC = medio insula cortex, S1 = somatosensory cortex, ACC = anterior cingulate cortex, FEF = frontal eyefields, IPS = intraparietal sulcus, IFG = inferior frontal gyrus, V1 = primary visual cortex, V2 = secondary visual cortex, PCC = posterior cingulate cortex, aMPC = anterior medial prefrontal cortex.

Yerkes–Dodson arousal curve. Based on primate research, The Yerkes–Dodson arousal curve is an empirical relationship between arousal and performance, originally developed based on the law of Yerkes and Dodson (1908). Generally put, the curve describes how performance increases with the energizing effect of arousal. Once levels of arousal become too high, performance decreases. Negative effects of arousal on cognitive processes presumably mediate these performance declines. However, dependent on the task requirements, the shape of the curve can be highly variable and even linear, for example for tasks demanding high persistence and motivation.

Small baseline pupil diameter and increased phasic task-evoked dilations have been proposed to correspond to task-relevant effortful processing [69]. We speculate that error awareness corresponds to engagement whereas error blindness corresponds to disengagement. In case of error awareness we may then hypothesize a linear increase in pupil dilation that co-varies with a linear increase in engagement. By contrast, tonically enlarged pupil diameter (as compared to normalized baseline) before a task-relevant event and reduced phasic task-evoked pupil dilations have been associated with overt indications of task disengagement [29]. Thus, in the unaware error condition, a chronically increased pupil (as compared to baseline pupil across the whole task) before the error, accompanied by reduced phasic responsiveness, may be hypothesized to reflect *disengagement* from the task. Hence, in case of error blindness, the pupil is hypothesized to have reached the ceiling of the U-function. A linear decrease in task engagement would not be reflected in a linear decrease (or increase) in pupil diameter.

Moreover, in line with this engagement/disengagement interpretation of the pupil pattern prior to aware errors and unaware errors respectively, and with previous observations in the field of sleep research [73], we observed that unaware compared to aware errors were associated with larger low-frequency oscillations from 2 s prior to 2 s after the unaware error.

Although pupil oscillations are largely unexplored within cognitive tasks, during states of sleep deprivation slow pupillary oscillations have been found to be associated with decreased levels of alertness and increased daytime sleepiness. The underlying cause of the increased pupillary oscillations observed in less alert and sleepy subjects is presumably an unstable drift of central sympathetic activation [72,73]. The current results show that low frequency pupil oscillations are not only related to a subjectively reported decrease in vigilance but also to unaware errors.

During incorrect responses, participants initially move their gaze toward the light stimulus, whereas on correct trials, this is not the case.

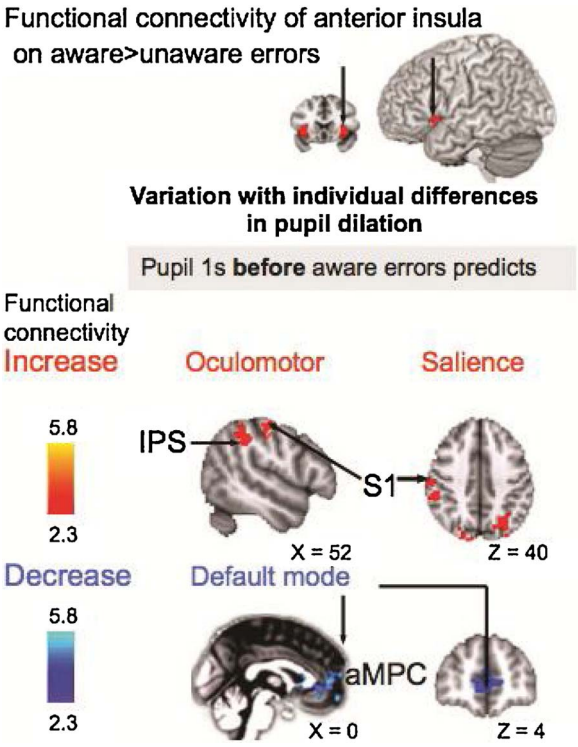

Fig. 4. Links between anterior insula's functional connectivity and pupil diameter for aware errors. Increased functional connectivity of anterior insula with oculomotor task control structures and decreased functional connectivity of anterior insula with areas of the default-mode network are predicted by pupil diameter 1 s before aware errors. The spatial distribution of correlation coefficients (z-scores) shows both positive correlations (red and yellow voxels) and negative correlations with preparatory pupil diameter (blue voxels) at cluster-corrected statistical thresholds of z = 2.3, p = 0.05. For a full list of activated regions, see Table 2. Note: S1 = somatosensory cortex, IPS = intraparietal sulcus, aMPC = anterior medial prefrontal cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Brain regions in which functional connectivity with anterior insula cortex during aware errors varied with pupil diameter before aware errors.

Brain regions in which functional connectivity of AIC during aware errors > unaware errors, covaried with pupil diameter 1 s before aware errors				
Positive covariance cluster corrected at z = 2.3, p = 0.05				
Brain region	X	Y	Z	Max z
R Postcentral gyrus (primary somatosensory cortex BA2R, BA1R, BA3bR)	64	−18	38	3.41
R Anterior intraparietal sulcus	42	−46	56	2.91
L Parietal occipital junction (superior parietal lobe/lateral occipital lobe)	−32	−62	34	3.50
Negative covariance, cluster corrected at z = 2.3, p = 0.05				
R Anterior medial prefrontal cortex	6	52	2	2.77
L Medial prefrontal cortex	−14	42	−6	3.43
L Frontal pole	−4	60	12	2.76

Coordinates are given in MNI space.

Note that this differential movement toward the light stimulus might systematically influence the size of the pupillary light reflex, which would constitute a confound if we contrasted correct to incorrect trials. Such a confound does not affect our analyses however, since we focus our analyses exclusively on the contrast of aware and unaware errors.

Taken together, the absence of task-appropriate pupil modulation during error blindness was evident in two measures of pupil diameter: in the baseline and error-evoked pupil diameter results, and in the diameter oscillation results, with more power in low-frequency oscillations immediately before and after unaware errors (Fig. 1b). The pupil pattern prior and subsequent to aware errors can be interpreted as task-synchronized arousal levels. These task-synchronized arousal levels reflect that the participant is engaging in the task at hand. Unaware errors in contrast were characterized by unstable desynchronized arousal levels before and after committed errors; this error blindness can be argued to reflect disengagement from the task, perhaps due in part to attentional lapses, to which continuous attention tasks are particularly vulnerable.

4.2. BOLD activation, functional connectivity, and their relation to pupil diameter changes during error awareness

Aware compared to unaware errors yielded significantly increased activation in right anterior insula, bilateral somatosensory cortex, thalamus, areas in the anterior cingulate, frontal eye fields and intraparietal sulcus. Analyses of functional connectivity showed increased functional connectivity of the anterior insula with bilateral somatosensory cortex and bilateral intraparietal sulcus.

It should be noted that for the covariation analyses of the neural response during aware errors as compared to unware errors with the pupil dilation measures in the 1 s window before aware errors, no aware-unaware subtraction took place in the *pupil* data. The fMRI analyses focused on how the *BOLD contrast aware > unaware errors* covaried with baseline-corrected *pupil values during aware errors* exclusively. This may sound puzzling at first, as one may argue that an aware/unaware contrast in the BOLD response should be matched to an aware/unaware contrast in the pupil response. However, our rationale for using (baseline-corrected) pupil diameter in aware error trials only was rooted in our theoretical interpretation of the physiological characteristics of the pupil response.

In the *aware* error condition, the phasic variation in pupil dilation was hypothesized to reflect task *engagement*. Phasic increases in diameter were taken to reflect increased engagement. So here we hypothesize a linear increase in pupil dilation that co-varies with a linear increase in engagement. In the unaware error condition, however, a chronically increased pupil, accompanied by reduced phasic responsiveness, was hypothesized to reflect *disengagement* from the task. Thus, for unaware errors, an linear decrease in task engagement would not be reflected in a linear decrease (or increase) in pupil diameter.

The two physiological parameters of the pupil response in the aware and unware condition may thus reflect different underlying processes. Since the pupil responses during unaware errors do not follow a linear de/increase with task (dis)engagement, we cannot use pupil response data from unaware errors as a linear regressor for the BOLD response. Instead, based on the considerations expressed above, we used the pupil response data from aware errors as linear regressors to predict the BOLD response during aware (as contrasted with unaware) errors.

In a covariation analysis, the pupil dilation measures during error awareness explained significant proportions of variance in the neural data. Individual differences in pupil diameter before the aware error predicted *increased* BOLD activation in motivational salience processing areas (anterior insula, rostral cingulate zone, somatosensory cortex) and in oculomotor control areas (frontal eye-fields, intraparietal sulcus) as well as increased functional connectivity of the anterior insula with other salience processing areas (somatosensory cortex) and with oculomotor control areas (intraparietal sulcus). Individual differences in pupil diameter before the aware error predicted *decreased* BOLD activation in areas of the default mode network (viz. anterior medial prefrontal cortex/frontal pole, posterior cingulate cortex, precuneus) and a decrease of functional connectivity of the anterior insula cortex with default mode network areas (anterior medial prefrontal cortex/frontal pole).

This suggests that, when added to the neural analyses, the pupil patterns can be interpreted as revealing signs of task engagement in the BOLD signal (decrease of default mode areas and increase of oculomotor areas during aware errors as compared to unaware errors). The decrease in default mode areas during error awareness was not manifest when computing the contrast aware versus unaware errors without taking pupil patterns into account. This widespread neuro-autonomic pattern, with increases in task-related oculomotor- and salience processing areas and concomitant decreases of activation in default mode network areas, seems well suited to prepare the individual to respond to the changed requirements after the detection of an error, by recruiting the necessary mental as well as physical efforts.

Based on the postulated mechanisms underlying pupil dilation during changes in cognitive control state [29,47], the observed neuro-autonomic pattern during error awareness seems to reflect a widespread pattern of increased task engagement and increased alertness during aware as compared to unaware errors. Signs of pupillary disengagement during unaware errors on the other hand, may be associated with a failure in neural systems to disengage the default mode network and generate a state of heightened activity in task-related structures. This observed widespread neuro-autonomic pattern is line with the postulated role of the LC in the ascending reticular activating system [38], which controls the level of activity of the whole brain, and has been shown to mediate transitions from relaxed wakefulness to periods of increased alertness and attention [40].

Overall, the current data provide evidence that the insula engages in large-scale networks during shifts in awareness states, and that these inter-regional interactions of the insula cortex during error awareness are mediated by autonomic arousal. Autonomically mediated changes in brain connectivity have previously been observed in human attentional fronto-parietal brain systems [7]. For example, a noradrenergic challenge produced differential effects on brain connectivity during rest (when low arousal is presumed) compared to during task performance. The current results illustrate that this relationship between autonomic processes and functional brain connectivity extends to cognitive operations on small timescales within a task.

4.3. Anterior insula's neural networks during error awareness

The ability to prioritize actions in response to dynamically changing circumstances constitutes an essential facet of adaptive and versatile behavior. Such cognitive control depends critically on the exploration of the internal and external milieu for alerting events that may require appropriate adaptive action. The integration of motivation and control is essential to understand how adaptive control works [32,43,58]. Motivationally salient action options activate the networks involved in coordination for action [6]. A motivational salience network, with the anterior insula cortex and anterior cingulate cortex as core nodes, transforms salience signals into an orienting response which serves to recruit the necessary physiological arousal, and to engage task-relevant fronto-striatal action control networks while disengaging task-negative networks (for review see [57,68]).

Overall, the present results suggest a relation of changes in the bodily periphery during error awareness with changes in the activation and functional connectivity of these networks. The observed functional connectivity between the anterior insula and the parietal oculomotor structures (intraparietal sulcus) is in line with human diffusion tensor imaging tractography demonstrating fiber tracts between anterior insula and parietal cortex, specifically the intraparietal sulcus [67]. The observed dichotomous functional connectivity-profile of anterior insula

cortex (positive relation with task-related networks/negative relation with areas of the DMN) during aware as compared to unaware errors is consistent with a recently proposed network model of anterior insula function [45]. These authors suggested that the anterior insula regulates the balance between default mode and task-specific control networks. They found that during effortful task engagement, functional connectivity of the anterior insula increased with task-specific control networks and decreased with the default-mode network [20,19,60,62,66]. Task-focused control networks are generally thought to be engaged when attention is focused on the task. The default-mode network, in contrast, is believed to participate in a self-referential state of brain function that is suspended during task engagement [19,27,30,31,54]. This balance between the default mode and task-focused control networks has been found to predict attentional lapses and performance variability [22,39,65,70]. The current results extend the previously observed shifts between task-related and default mode networks during variations in performance efficiency (specifically [22,39,70] by suggesting that such shifts vary with task-related changes in the body-periphery as indexed by pupil diameter.

4.4. The role of the anterior cingulate cortex

The awareness of errors engendered co-activation of the anterior insula and the anterior cingulate associated with awareness-related pupil dilation. This is in line with previous observations in a Stroop task [15]. In that study, pupil dilation and corresponding activity in the anterior insula, mediofrontal cortex, and pre-supplementary motor area increased during the commitment of performance errors. The neural pattern was interpreted by the authors as potentially reflecting awareness of the performance error. This interpretation was confirmed by direct evidence in the current study. Together these results support a model postulating that the anterior insula integrates salient events with autonomic information [8,9,57]. These findings also revealed more activation of dorsal anterior cingulate with more autonomic engagement during aware error processing. Indeed, patients with dorsal anterior cingulate damage are impaired at regulating sympathetic outputs with increasing task effort [14].

In a review of 107 studies, Paus and colleagues [52] found the dorsal anterior cingulate activated during non-specific behavioral effort. Similarily, Raichle and colleagues [54] pointed in the same behavioral context to decreases in activation of the ventromedial prefrontal cortex and subgenual cingulate. Dorsal and subgenual portions of the anterior cingulate may be functionally dissociated with respect to autonomic drive and cognitive effort: Whereas the dorsal anterior cingulate is associated with autonomic up-regulation during increased task effort when people are engaged in demanding tasks [13], the subgenual cingulate has been related to resting state and to autonomic control centers involved in sleep [11]. In line with these findings, awareness-related pupil responses in the current study were inversely linked to the dorsal and subgenual parts of the anterior cingulate (Fig. 3). The current results suggest that this functional dissociation of dorsal and subgenual cingulate with respect to autonomic arousal also applies to rapid cognitive operations when cognitive engagement and its associated autonomic nervous system activity fluctuate.

4.5. Limitations and strengths of the current study

One strength of the current approach is the combination of pupil diameter with functional brain networks, which has to our knowledge not been undertaken before. As discussed previously, pupil dilation changes have previously been related to error-commission and insula activation [15]. However, the impact of changes in arousal levels on cognitive tasks has only been considered in few functional neuroimaging studies, and mainly in selective attention tasks [5,17]. The simultaneous objective acquisition of vigilance and arousal levels during neuroimaging studies has up to now mainly been the domain of sleep research, or research on sleep deprivation. Another strength is the covariation with activation and insula networks at the whole-brain level, revealing the potential of the pupil measurement to explain not only variance in activation increases in task-related local BOLD activation within the insula, but also variance in activation decrease in areas of the default mode network.

Previous work on error awareness often employed only a motor response on error detection. In the present paradigm, subjects press a button on each trial (the left/right button, randomized across subjects) during the evaluation to evaluate their antisaccadic response. Thus, subjects press a button during aware and during unaware errors; hence, the motor response is kept equal across aware and unaware error-types, allowing for an unconfounded analysis of the mechanisms of error awareness and error blindness.

Despite these advantages, a number of potential limitations may apply.

First, while this study suggests a relationship between changes in arousal level and the neural networks underlying error awareness, the directionality of the effect is not clear. The methodology used cannot disentangle afferent and efferent contributions to the observed changes in arousal, nor does it provide information on the directionality of the neural network pathways, or to provide firm conclusions about temporal relationships between arousal and neural responses. Generating the appropriate level of preparatory autonomic activity might be viewed as a goal state [36], serving to disengage the default mode network and energize control structures to render the system ready to process and respond to salient information. Thus, physiological arousal may mediate differences in large-scale network changes between aware and unaware errors. Alternatively, a transient state of task disengagement might incur a failure of timely network configuration and, consequently, a failure to mobilize task-adequate levels of bodily arousal. Thus, neural activity/connectivity changes may mediate the changes in autonomic state. Hence, these findings cannot conclusively position the insula and pupil responses as precursors to the emergence of awareness. It seems equally plausible that both phenomena are rather sequelae to awareness − that is, that an orienting response is evoked in the insula and reflected in pupil size, only once an error has been detected. The causal direction of this effect remains to be determined.

Second, aware and unaware errors might be associated with different types of saccadic eye movements. Indeed, unaware errors were corrected more frequently than aware errors, as has been observed previously. This opens the possibility that the observed difference in pupil diameter and brain activity are more related, beyond error awareness per se, to the correction of erroneous eye movements. However, the pupil signal in the pre-target window is not sensitive to error-correction taking place later in time. Yet, due to sluggishness of BOLD response, error correction might still affect target-related BOLD signals. Note however that to the extent that this is the case, the differential effects of error correction should express themselves primarily in the oculomotor network (with more activation for unaware errors), and (importantly) not in the error awareness/salience network.

Third, a metric of pupil size relative to the mean pupil value across the entire task may be affected by individual differences in psychophysical features of the pupil time-series; and such inter-individual variability might render the outcome of the covariance-based fMRI analyses (based on individual differences in pupil responses) uninterpretable. We acknowledge the suggestions of an anonymous reviewer who brought up these important issues. The most important of such potential confounds will be summarized below, along with either a concession of potential implications, or our reasons to believe that our analysis results were not susceptible to these confounds. (1) The luminary properties of the visual field change once the imperative stimulus sets in; on error trials but not during correct responses, the subjects initially move their gaze toward the light stimulus at first, thus systematically influencing the magnitude of the pupillary light reflex [71]. Since we did not contrast correct versus incorrect trials, our

outcomes should not be affected by this potential confound. (2) During unaware errors, initial saccadic amplitudes are often smaller than during aware errors; hence, the pupil response should be less affected by the luminance of the target stimulus during unaware errors. Furthermore, any deviation away from fixation will systematically affect measured pupil size, and hence contaminate aware vs unaware comparisons (via the presumed difference in saccadic amplitudes between these trial-types). Since we contrasted pupil responses during aware versus unaware errors, these pupil findings should be interpreted with some caution. The effects of error awareness vs. blindness might in these cases be confounded, at least to some extent, by systematic effects of saccadic amplitudes on pupil size. (3) To the extent that these confounds and constraints apply to our analysis of pupil data, they might also affect our covariance-based fMRI results that are based on individual difference in pupil responses during error awareness. If individual differences in psychophysical features of pupil responses covary with those in pupil responses related to error awareness, then our fMRI results are confounded and difficult to interpret. However, we argue that the potential of these confounds to affect our covariance-based fMRI outcomes seems much more limited. (3a) These analyses are based only on pupil data from a one-second window preceding the error, which are least susceptible to such psychophysical confounds because the confounder processes take place mostly during the eye movement that constitutes the error. (3b) These confounds may hold the strongest potential in the aware-unaware contrast of the pupil data, which we do not use for covariance-based fMRI (instead, we use the pupil response during error trials as the regressor of interest − see also the eighth limitation discussed below). (3c) The sources of individual differences in such confounding factors, although systematic, should be entirely unrelated to the underlying processes of error awareness and motivational significance; at best, they should show in the engagement of brain areas involved in lower-order oculomotor control, which doesn't appear to be the case. The outcomes show that individual differences in pupil responses preceding aware errors predict the extent to which the anterior insula is recruited, and the extent to which the insula manages to recruit higher-order oculomotor centers (FEP, IPS) (and deactivate DMN centers), more so in aware than unaware errors. This complex pattern is exceedingly difficult to reconcile with an origin in systematic inter-individual variability in psychophysical aspects of pupil responses that are entirely distinct from processes such as motivational salience.

Fourth, for functional connectivity, the shift in balance varied with patterns of pupil diameter before the aware error. Given that the timing of the BOLD response is not very informative about the timing of the neural responses, it is difficult to disentangle whether the pupil diameter 1 s before the aware error precedes or follows error-related BOLD changes or whether they started concurrently. Additional studies, e.g., using MEG, are needed in order to further address the differential timing of autonomic responses with respect to anterior insula function and network changes.

Fifth, it should be noted that an analysis of *intra*-individual differences combined with an analysis of trial-by-trial fluctuations in pupil diameter during aware errors could have been highly informative in principle; however more trials are needed in the aware/unware condition, which is not yet feasible in the experimental designs that are currently available for error awareness. Also, the jittered design with null-events that we used here is highly advantageous for the temporal resolution of BOLD signal when estimating stimulus-locked BOLD response in a multiple regression framework Miezin et al., 2000, yet it impairs considerably the assessment of trial-to-trial performance adaptations. We chose not to go there, also because a previous study of pupil dilation evoked by errors (reported by [15]) showed that there was no consistent trial-by-trial relationship between pupil diameter, error percentage or post-error slowing. This question might benefit from future BOLD studies of error awareness that allow more explicitly for analysis of intra-individual differences.

Sixth, in the current experiment we used covariance-based neuroimaging which has by now become more or less mainstream. Entering relevant co-variates as regressors into the model for the BOLD signal serves to reduce error variance and, most of the time, serves to prune excessive patterns of activation so that only those activations that actually scale with the relevant parameters light up. For the present case, the argument would be that inter-individual variability in pupil reactivity corresponds to individual differences in task (dis-)engagement. Task engagement should be supported by the recruitment of physiological arousal, which is expressed in pupil reactivity. Of course the causal relationship could go two ways: lack of task engagement results in reduced error awareness, or lack of error awareness results in lack of recruitment of arousal. The present approach is correlational in nature and cannot, as noted above, address this issue of causality.

Seventh, covariance-based fMRI assumes linear relationships between regressors and the BOLD signal. Thus, if we assume that individual differences in the regressor-metric of interest represent individual differences in a specific underlying psychological process of interest, then we must be able to argue that the regressor-metric maps linearly onto the psychological process. In our case, we assume that the pupil response (as the metric used as regressor) reflects the underlying process of task engagement. We have speculated that error awareness and blindness correspond to task engagement and disengagement, respectively. Task engagement has been proposed to correspond to small baseline pupil diameter and increased phasic task-evoked dilations [69]. By contrast, task disengagement has been proposed to correspond to tonically enlarged pupil diameter in combination with reduced phasic task-evoked pupil dilations [29]. Thus, for error awareness we may hypothesize that a linear increase in engagement co-varies with a linear increase in pupil dilation; by contrast, for error blindness, we may hypothesize that a linear decrease in task engagement is reflected in a U-shaped pupil response. As a consequence, we cannot use pupil response data from unaware errors as a linear regressor for the BOLD response, and hence cannot directly infer how error blindness is expressed in patterns of functional brain activity and connectivity. Still, pupil response data from aware errors can be used for covariance-based fMRI, and hence does allow us to infer at least the neural bases of error awareness. If metrics may be obtained that scale more linearly with error blindness, then future work may examine the corresponding neural mechanisms more directly.

Eighth, and lastly, some researchers have proposed that error awareness can best be understood from an evidence-accumulation perspective [68,75]. That is, from the moment that an action is initiated, until after the action is finished, different channels provide accumulating evidence on whether the action is successful or fails. The error awareness antisaccade tasks relies on accumulating evidence from proprioception and sensory (visual) input to set evidence for error awareness. Participants evaluate their performance after each trial. The presumed reason why the antisaccade task induces sufficient numbers of unaware errors pertains to the fact that the error signal from proprioception and sensory (visual) input is fairly weak for short and immediately corrected prosaccades [68]. In order to evaluate if an action is successful or fails, evidence is evaluated as to whether it predicts an action outcome that matches or differs from what is intended. As a result, the accumulating evidence from proprioception and sensory (visual) input holds the potential to set evidence for error awareness.

In other tasks aimed at studying error awareness, partly different sets of brain regions may be related to the awareness of errors. This may depend on the processes involved in accumulating evidence of erors. Such processes may primarily involve perception (such as in contrast-masking tasks; [76,77]), proprioception (such as in antisaccade tasks [25,49,71]), or rule representations (such as in adjusted go-nogo tasks, where several rules have to be monitored continuously; [34]). Activation related to error awareness has mainly been observed in the anterior part of the insula [41], which may be characterized by a functional anterior-posterior gradient [39]. Anterior parts are presumed to involve

cognitive, (social) emotional processes, and peripheral physiological changes; middle parts are thought to relate to sensory processes; and posterior parts to sensory-motor processes (for a meta-analysis see [78]). Whereas the current task and the current BOLD-pupil covariation analysis involved anterior regions of the insula, potentially reflecting involved peripheral physiological changes, other error-awareness tasks (without pupil-related covariates) that capitalize on other processes of error awareness may elicit more activation in other (e.g., sensory-related) areas of the insula.

4.6. Potential clinical implications

Based on our findings in healthy volunteers, one could propose that synchronized behavior-pupil relations might not be present in patients with deficits in error awareness. This hypothesis is in line with investigations of error awareness in ADHD, where autonomic arousal has been shown to be blunted during error awareness [50]. One may speculate that deficits in error awareness may be associated with a deficit in the ability to synchronize autonomic and cognitive states. Desynchronized arousal may be reflected in the loss of strict negative correlation between task-positive and task-negative default mode activation. Such default-mode brain dysfunction has been observed in pathologies including ADHD, schizophrenia, addiction, and frontotemporal dementia [4,18,50,63,66]. Whether desynchronized pupil-behavior relationships may constitute an index for disintegrated relations between task-related processes and processes in areas of the default mode network would be an intriguing question for future research.

5. Conclusion

To conclude, the current data provide a direct link between the awareness state, the neural activity and connectivity of insular cortex, and the associated variability in peripheral autonomic response measures. Anterior insula networks shifted between task-related brain structures and default mode systems and co-varied with the physiological arousal system. These results advance our understanding of anterior insula network function and of dissociations between aware and unaware processing. During events that require our increased attention and awareness the peripheral processes of the autonomic nervous system seem to relate to large-scale network changes. If we interpret the data based on the postulated mechanisms underlying pupil dilation during cognition, the observed widespread neuro-autonomic patterns during error awareness and error blindness seem to reflect increased task-engagement during aware as compared to unaware errors. This widespread neuro-autonomic pattern in task-related areas and the suppression of DMN areas, seems well suited to prepare the individual to respond to the changed requirements after the detection of an error, by recruiting the necessary mental as well as physical effort.

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