Behavioral/Cognitive

Sensorimotor Cortex GABA Moderates the Relationship between Physical Exertion and Assessments of Effort

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Experiences of physical exertion guide our assessments of effort. While these assessments critically influence our decisions to engage in daily activities, little is known about how they are generated. We had female and male human participants exert grip force and assess how effortful these exertions felt; and used magnetic resonance spectroscopy to measure their brain GABA concentration. We found that variability in exertion (i.e., the coefficient of variation in their force exertion profile) was associated with increases in assessments of effort, making participants judge efforts as more costly. GABA levels in the sensorimotor cortex (SM1) moderated the influence of exertion variability on overassessments of effort. In individuals with higher sensorimotor GABA, exertion variability had a diminished influence on overassessments of effort. Essentially, sensorimotor GABA had a protective effect on the influence of exertion variability on inflations of effort assessment. Our findings provide a neurobiological account of how the brain's GABAergic system integrates features of physical exertion into judgments of effort, and how basic sensorimotor properties may influence higher-order judgments of effort.

Key words: **effort; exertion; GABA; sensorimotor cortex**

Significance Statement

Feelings of effort critically shape our decisions to partake in activities of daily living. It remains unclear how the brain translates physical activity into judgments about effort (i.e., "How effortful did that activity feel?"). Using modeling of behavior and neuroimaging, we show how the nervous system uses information about physical exertion to generate assessments of effort. We found that higher variability in exertion was associated with increases in assessments of effort, making participants judge efforts as more costly. GABA, the brain's main inhibitory neurotransmitter, moderated the influence of exertion variability on overassessments of effort. These findings illustrate how low-level features of motor performance and sensorimotor neurochemistry influence higher-order cognitive processes related to feelings of effort.

Introduction

Assessments of effort shape our decisions to engage in physical activity. For example, after performing an exercise (e.g., lifting weights, running, cycling), we evaluate how effortful it felt and use this information to decide our next course of action, whether it be performing exercises of similar intensity, switching to a more strenuous level, or taking a break. Previous work has suggested that GABAergic function influences motor performance by suppressing activity in the motor cortex to produce more efficient behavior (Coxon et al., 2006; van den Wildenberg et al., 2010). Increased GABAergic concentration in the sensorimotor cortex (SM1) has also been associated with improved perceptual acuity (Puts et al., 2011; Kolasinski et al., 2017). Despite these fundamental studies of the role of GABA in sensorimotor

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performance and perception, little is known about the neurobiological mechanisms that transform physical exertions into assessments of effort.

Previous studies of the neurobiological basis of sensorimotor performance have shown that an individual's SM1 GABA concentration is related to their motor cortex activations (Stagg et al., 2011), and influences both sensory acuity (Puts et al., 2011; Kolasinski et al., 2017) and motor learning (Stagg et al., 2011; Kolasinski et al., 2019). It has been proposed that GABA modulates these functions by inhibiting unwanted neural firing and sharpening the tuning of neuronal responses. In this framework, GABA may enhance the signal-to-noise ratio of sensorimotor output, which improves the fidelity of sensorimotor representations.

Recent work has begun to identify how low-level features of the motor system are related to judgments about effort (Galaro et al., 2019; Hogan et al., 2020; Umesh et al., 2020). Anatomical properties of the motor cortex (Umesh et al., 2020), and underlying motor cortical physiology (Galaro et al., 2019; Hogan et al., 2020), have been associated with individuals' subjective valuation of effort and effortful output. Furthermore, variability in motor performance has been related to judgments of effort, such that increased variability served to reduce individuals' willingness to perform an action (Salimpour and Shadmehr, 2014; Salimpour et al., 2015).

Here we investigate the behavioral processes responsible for evaluating levels of effort following sustained physical exertion, and how these processes are influenced by the brain's sensorimotor neurochemistry. We hypothesized that discrepancies between force exertions and assessments of effort arise from variability in motor performance. This hypothesis is motivated by studies of effort-based decision-making which have suggested that increased exertion variability (EV) is associated with increased effort costs (Salimpour and Shadmehr, 2014; Salimpour et al., 2015). EV may increase uncertainty in performance outcomes, and act as an added cost that inflates assessments of effort. Given that increased sensorimotor GABA has been associated with both modulating motor variability and performance (Stagg et al., 2011; Kolasinski et al., 2019), and increasing perceptual acuity (Puts et al., 2011; Kolasinski et al., 2017), we hypothesized that GABA may influence the relationship between EV and subjective assessments of effort. Importantly, a recent study of visual perception found a similar relationship by which GABA influenced the interaction between visual processing and judgments of visual stimuli (Frangou et al., 2019). This result in the visual system further suggests a general role for GABA in mediating the relationship between sensory processing and perception.

Materials and Methods

Experimental setup

Custom MATLAB (http://www.mathworks.com) scripts implementing PsychToolBox libraries (Brainard, 1997) were used to present visual stimuli and acquire behavioral data. A hand clench dynamometer (TSD121B-MRI, BIOPAC Systems) was used to record grip exertion. Signals from the dynamometer were sent to our custom software for real-time visual feedback of participants' effort exertion. Effort exertion trials were performed with the force transducer in the participants' hand while in an upright sitting position.

Experimental procedures

Participants. All participants were prescreened to exclude those with prior history of neurologic or psychiatric illness. The Johns Hopkins School of Medicine Institutional Review Board approved this study, and all participants provided informed consent. Thirty-one individuals (mean age, 23.8 years; age range, 18-30 years; 15 females, 4 left-handed) participated in the main experiment, none of which were ultimately excluded from the final analyses. The sample size for this study was informed by previous studies from our group that used the same paradigm to study the relationship between effort valuation and brain signals (Hogan et al., 2019, 2020, Umesh et al., 2020).

To independently replicate the behavioral results from the main experiment, we analyzed data collected in previous experiments performed in our laboratory (Hogan et al., 2019, 2020). None of the participants in this replication overlapped with the 31 participants in the main study group. A total of $N = 39$ participants were included in this replication (mean age, 22.8 years; age range, 18-34 years; 16 females), none of which were excluded from the final analyses. The previously published analyses of this data focused on choice behavior following the Association and Assessment Phases, the analysis of effort assessment (EA) behavior was not reported in either the main text or the supplemental materials of those previous papers (Hogan et al., 2019, 2020; Umesh et al., 2020).

Experimental paradigm. Participants were informed that they would receive a fixed show-up fee of $30 and that this fee did not depend on performance or behavior during the experiment. In the initial stage of the experiment, each participant was verbally instructed to squeeze the hand clench dynamometer with their maximum force for three consecutive repetitions. The maximum of these exertions was selected to be the participant's maximum voluntary contraction.

Next, participants underwent an Association Phase where they were trained to match effort levels with forces exerted on the dynamometer. Effort levels ranged between 0 (no exertion) and 100 (force equal to 80% of the participant's maximum voluntary contraction) effort units (Fig. 1*A*). A trial began with the numeric display of the target effort level, followed by an effort gauge in the form of a black vertical bar. The gauge filled up with a white bar as participants exerted against the dynamometer. The bottom and top of the gauge represented levels 0 and 100 effort units, respectively. On a given trial, participants were instructed to reach a target zone (defined within 5 effort levels of the target) as fast as possible and maintain that exertion level. The target zone was visually marked with green if the exertion level was maintained. A single trial lasted for 4 s. At the end of exertion, a success screen was presented if participants were within the target zone for more than two-thirds of the time (2.67 s), and a failure screen was presented otherwise. During the Association Phase, participants were presented with 5 trial blocks that contained a target level, which varied from 10 to 80 U in increments of 10 U. One minute of rest was given between each training block to ensure participants did not become fatigued during the Association Phase. We did not perform this paradigm at the highest exertion levels to ensure that participants would not become fatigued. Training blocks were presented in a randomized order.

Finally, participants performed an effort Assessment Phase to test how well they were able to assess their level of exertion (Fig. 1*B*). During trials in this phase, participants were asked to retrospectively estimate their subjective perception of the cost required to mobilize their physical force during a preceding epoch of exertion. Each assessment trial began with a black horizontal effort gauge that participants were instructed to fill completely, and hold, by exerting on the force transducer dynamometer. Participants were given 4 s to exert. Unlike the Association Phase, the end of the effort gauge did not represent 100 effort units. Instead, it represented the target effort level selected from the range 10-80 effort units, incremented by 10 effort units. In this way, participants were not given explicit feedback of the units of effort associated with their exertion. Following this exertion, participants were presented with a number line marked from 0 to 100 effort units and instructed to select the effort level that they believe that they had just exerted. They moved a cursor along the number line using two buttons and selected an effort level using a third button. Participants were tested on 48 trials, with 6 trials for each effort level from 10 to 80 effort units. These effort levels were presented in a random order; no feedback

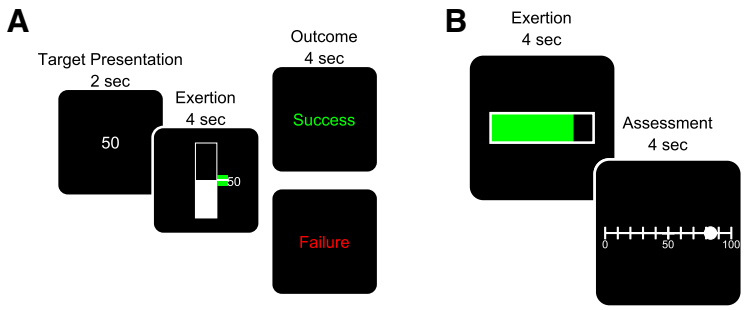

Figure 1. Experimental design. ***A***, Association Phase. Participants were trained to associate numeric effort levels with force exerted on a hand clench dynamometer. Effort levels ranged from 0 (no force) to 100 (80% of maximum grip force) effort units. Each trial began with presentation of the target, followed by an effortful grip with real-time visual feedback of the exerted force represented as a bar that increased in height with increased exertion. A green visual cue was also displayed, within which participants were instructed to maintain their exerted effort. Feedback of success or failure was provided at the end of each trial. ***B***, Assessment Phase. Participants were instructed to fill a horizontal bar by gripping the transducer. On each trial, the full bar corresponded to a target effort level. The explicit units of effort associated with filling the bar were not presented. Successfully achieving the effort target resulted in the bar turning from red to green. Following exertion, participants selected the effort level they believed they had squeezed. No feedback was provided as to the accuracy of participants' assessed effort levels.

was given to participants regarding if they held their exertion at the target level for the allotted time, or the accuracy of their EAs.

It is important to reiterate that, when participants performed an EA in our experiment, they were instructed to estimate the effort they felt they exerted during the preceding exertion. EA required participants to retrospectively estimate their subjective cost of mobilizing the force/physical activity to achieve the goal of filling the exertion thermometer. In this framework, we refer to "effort" as participants' subjective rating of the physical activity to fill the exertion thermometer. We refer to "exertion" as the actual physical output a participant recruits during the exertion epoch. It should be noted that a previous study, using a similar paradigm involving the retrospective estimation of effort, used the same definitions of effort and exertion (Pooresmaeili et al., 2015).

Magnetic resonance spectroscopy (MRS) protocol. MRS data were acquired on a Philips 3 T Achieva MRI scanner (Philips Healthcare) using a 32-channel head coil. Before MRS data acquisition, a T1-weighted image (MPRAGE) was acquired for voxel placement and subsequent partial volume correction. MRS data were acquired using the HERMES sequence according to published work (Saleh et al., 2016). Measuring GABA using conventional MRS measures is problematic because of the low concentration of GABA in the human brain (1-2 mM) and overlap of the GABA signal from more concentrated metabolites, such as creatine. HERMES is a difference-editing technique that utilizes MEGA editing (Mescher et al., 1998) by applying frequency selective editing pulses that only affect the metabolite of interest. HERMES uses a 4-step editing scheme with Hadamard encoding, allowing for simultaneous and orthogonal measurement of GABA and glutathione (GSH; beyond the scope of this project) in a single acquisition, not possible using unedited MRS. Editing pulses were applied at 1.9 ppm for GABA and 4.56 ppm for GSH in the following order: A, $GABA_{ON}$ and GSH_{ON}; B, $GABA_{OFF}$ and GSH_{ON}; C, $GABA_{ON}$ and GSH_{OFF}; D, $GABA_{OFF}$ and GSH_{OFF}, which were repeated for ~11 min per region (320 transients in total, 80 transients per subexperiment). The difference Hadamard combination A + C − B − D (i.e., transients when the editing pulse was $GABA_{ON}$ minus transients when the editing pulse was $GABA_{OFF}$) resolves GABA signal as shown in Figure 2. Additional parameters were as follows: TE/TR 80/2000 ms, 20 ms editing pulses (cosine-modulated sinc-Gaussian for the dual band pulses and sinc-Gaussian for the single-band pulses), VAPOR water suppression (Tkac et al., 2007), 2 kHz spectral width with 2048 data points. Interleaved water reference correction was used to minimize B0 field drift. Twenty unsuppressed water averages were acquired for metabolite quantification.

Voxels were placed over the left primary SM1, right insula (rIns), and the occipital cortex (OCC) (Fig. 2*A*). The SM1 voxel ($30 \times 30 \times 30$ mm^3) was centered on central sulcus posterior to the hand region of the motor cortex and rotated to align with the edge of the brain. The center of the rIns voxel ($30 \times 35 \times 25$ mm^3) was aligned with the temporal-frontal junction and then moved toward the midline to avoid temporal cortex but also avoid ventricles (Fig. 2*B*). The voxel was subsequently rotated in the sagittal plane to align with the angle of the temporal-frontal junction. The OCC voxel ($30 \times 30 \times 30$ mm^3) was centered on the midline of the OCC (Fig. 2*C*). The bottom edge of the voxel was rotated to align with the cerebellar tentorium, and the anterior edge was aligned with the occipital/parietal junction. The voxel was never rotated beyond 45 degrees to avoid changes in chemical shift direction.

These neurochemical data were not time-resolved or EA-related (i.e., not collected at the time of the behavioral experiment), and acquisition from these regions of interest was counterbalanced in order across the group. These neurochemical data reflect the baseline neurotransmitter concentrations in each participant, and we collected each from a single voxel in the associated brain region. We focused our analysis on left SM1 because of its role in motor output. We chose the rIns as a control region because it has also been shown to encode proprioceptive and interoceptive sense and is active during effort valuation (Critchley et al., 2004; Hogan et al., 2020). We chose OCC as a control region because it is an area responsible for visual perception, which is independent of physical EA. Time constraints and methodological considerations precluded us from using further control regions. To study the neurochemical basis of EA, we related measured GABA levels to exertion and effort ratings.

MRS analysis. HERMES data were analyzed using Gannet 3.1 (Edden et al., 2014); 3 Hz line broadening and zero filling were applied. Frequency and phase correction were applied using Robust Spectral Registration (Mikkelsen et al., 2020) in the time domain by aligning each transient to a weighted average reference transient using nonlinear least-squares optimization. Weighted averaging was then used where poorer-quality transients are weighted less. Subsequently, the GABA and water signals were fit using the GannetFit module. The GABA-edited difference spectrum was then modeled between 2.79 and 4.10 ppm using a three-Gaussian function and a nonlinear baseline to quantify the 3.0 ppm GABA signal using nonlinear least-squares fitting. The water signal was modeled between 3.8 and 5.6 ppm with a Lorentzian-Gaussian function with phase and linear baseline parameters using nonlinear least-squares fitting. Subsequently, voxels were independently coregistered to the T1-weighted images and were subsequently segmented into gray matter, white matter, and CSF for each individual and each voxel within GannetCoRegister and GannetSegment models, using SPM12 (Ashburner and Friston, 2005). For quantification and partial volume correction of GABA levels, we used the tissue-corrected tissue correction from Gannet (Harris et al., 2015). GABA levels were expressed relative to the unsuppressed water signal accounting for tissue and metabolite specific T1 and T2 values, parameters for water visibility and editing efficiency. No SM1 datasets were excluded. For rIns, 2 participants did not have rIns data acquired, and a further 10 datasets were excluded because of high fit error (>20%), lipid contamination, or spurious water echoes. For OCC, 3 participants did not have OCC data acquired, and a further 2 datasets were excluded because of high fit errors (>20%) and spurious water echoes. As per quality assurance and reporting guidelines (Peek et al., 2020), no datasets were excluded from SM1, 12 datasets were excluded from rIns, and 3 datasets were excluded from OCC. FWHM for GABA (mean ± SD) were as follows: SM1, 21.33 ± 1.90; rIns, 22.61 ± 4.33; OCC, 21.87 ± 1.97. Fit errors (mean ± SD) were as follows: SM1, 8.87 ± 1.84; rIns, 10.71 ± 3.38; OCC, 5.26 ± 1.46. SNR (mean ± SD) was as follows: SM1, 10.01 ± 1.49; rIns, 12.08 ± 3.02; OCC, 14.04 ± 3.03. These quality metrics are in line with those reported in a large multisite edited MRS study (Mikkelsen et al., 2019). It should be noted that a large proportion of rIns data were excluded because of poor data quality. This region is problematic for shimming and has low SNR.

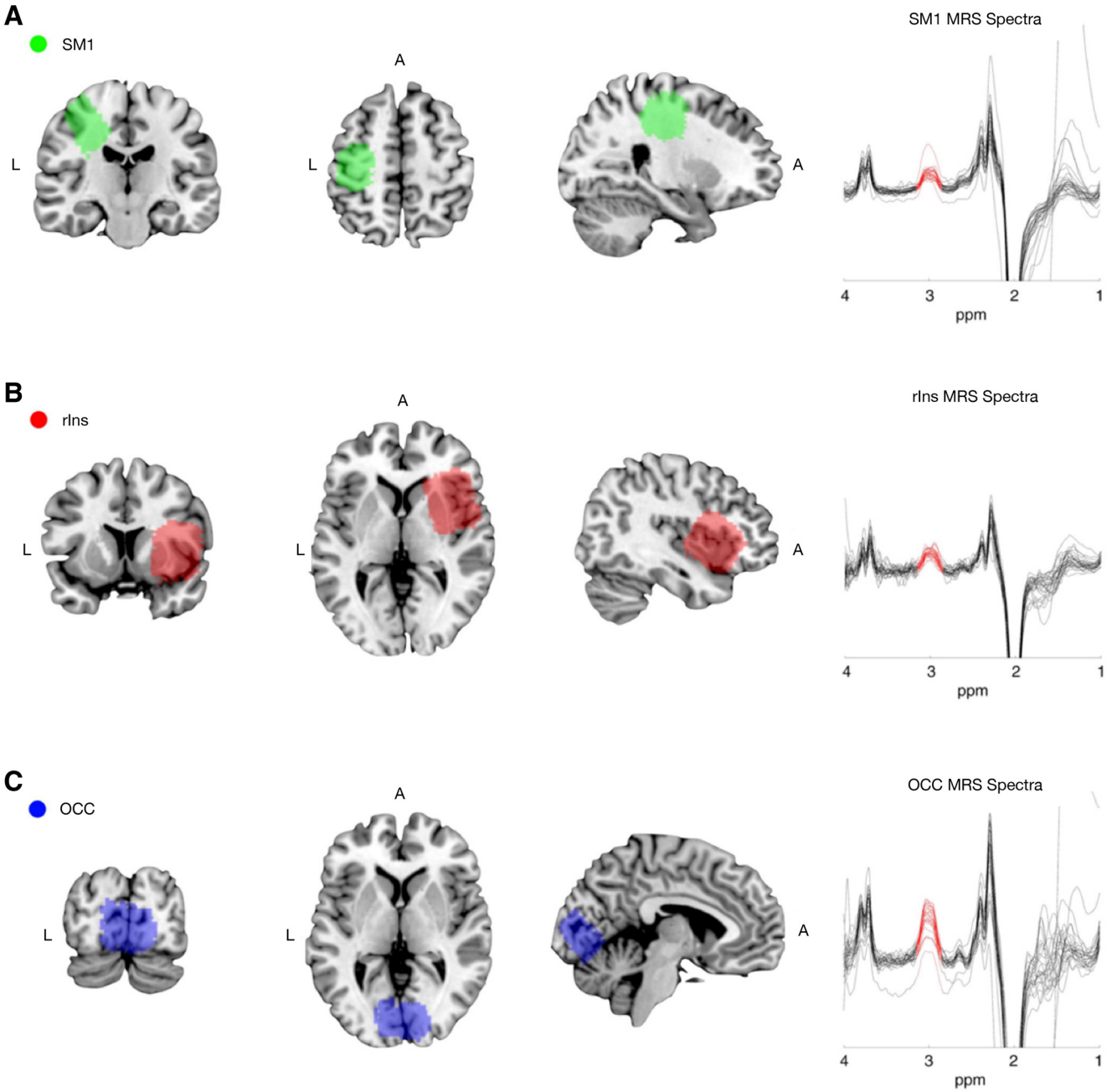

Figure 2. MRS voxel placement and spectra. Each participant took part in a scanning session in which we acquired MRS data. Three MRS acquisitions were performed to acquire data from voxels in SM1 (***A***; $n = 31$; green), rIns (***B***; $n = 26$, red), and OCC (***C***; $n = 17$, blue). We positioned the MRS voxels using anatomic landmarks on acquired structural scans to ensure that voxel placement was consistent across participants. The details for voxel placement acquisitions are in Materials and Methods. Here we illustrate the conjunction of participants' voxels overlaid on a template brain, and associated spectra. Axial section; L, left; A, anterior. We obtained high-quality difference-edited spectra for each ROI (right most panels), with a clearly distinguishable GABA peak (shown in red) at 3 ppm. Here we show spectra for all participants.

Data analysis procedures

Exertion and EA metrics. To analyze participants' exertion performance (i.e., the time of force exertion) during the Assessment Phase, we focused on the time period in which participants held the target exertion level. To exclude performance during the ramp to target effort level, and focus on the exertion hold period, we calculated metrics of performance for the final 2 s of the 4 s exertion segment (i.e., excluded the first two second of the exertion phase).

To evaluate mean exertion (ME) on a given trial, we calculated participants' ME during the final 2 s of the hold segment. To evaluate EV, we calculated the standard deviation (SD) of participants' exertion during the 2 s hold segment. We also calculated a normalized EV (EVN) metric in which we divided the SD of participants' exertion during the 2 s hold segment by their ME (i.e., the coefficient of variation of the EV). The normalized variability controlled for the relationship between increasing levels of exertion and EV so that we could evaluate how trial-to-trial variations in EV were related to assessments of effort.

We also calculated the assessment error (AE) on a given trial as the difference between the ME and EA on that trial. This metric provides a measure of the accuracy of participants' retrospective estimates of their subjective perception of the cost required to mobilize their physical force on a trial, relative to their actual exertion.

Models. We performed a series of hierarchal linear models to evaluate how participants' trial-to-trial variance in exertion performance was related to trial-to-trial variance in their ratings of exertion and basal SM1 GABA concentration. These analyses were performed using

MATLAB R2022a, using the *fitglme* function in the Statistics and Machine Learning Toolbox. We tested relationships between ME, EV, and EAs. These models included fixed effect (β_0, β_1) as well as random effects ($\beta_{0|PAR}$, $\beta_{1|PAR}$) for each participant.

$$\text{Model 1: } ME = (\beta_0 + \beta_{0|PAR}) + (\beta_1 + \beta_{1|PAR}) \cdot EV$$

$$\text{Model 2: } ME = (\beta_0 + \beta_{0|PAR}) + (\beta_1 + \beta_{1|PAR}) \cdot EA$$

To test how trial-to-trial discrepancies between participants' EAs and their ME (AE: the difference between ME and EAs) were related to their EVN. This model allowed us to test whether variability in exertion contributed to assessments of effort.

$$\text{Model 3: } AE = (\beta_0 + \beta_{0|PAR}) + (\beta_1 + \beta_{1|PAR}) \cdot EVN + (\beta_2 + \beta_{2|PAR}) \cdot E_{max} + (\beta_3 + \beta_{3|PAR}) \cdot trial$$

To account for relevant factors, this model also included participants' ME, maximum exertion E_{max}, and trial number trial. All variables were *Z*-scored before being entered into the regression, to allow for interpretation of standardized regression coefficients.

To evaluate the influence of basal SM1 GABA concentration on participants' EAs, we performed a GLM that included all factors in Model 3, as well as interactions between significant factors in Model 3 (i.e., trial and EVN). All variables were *Z*-scored before being entered into the regression, to allow for interpretation of standardized regression coefficients.

$$\text{Model 4: } AE = (\beta_0 + \beta_{0|PAR}) + (\beta_1 + \beta_{1|PAR}) \cdot EVN + (\beta_2 + \beta_{2|PAR}) \cdot E_{max} + (\beta_3 + \beta_{3|PAR}) \cdot trial + (\beta_4 + \beta_{4|PAR}) \cdot GABA_{SM1} + EVN \times GABA_{SM1}(\beta_5 + \beta_{5|PAR}) + trial \times GABA_{SM1}(\beta_6 + \beta_{6|PAR})$$

Model 4 is a version of a moderation analysis, which is a form of linear modeling in which correlations observed in experimental data are explained by assuming that specific causal influences exist among the variables (Preacher et al., 2016). Specifically, moderation is said to occur when the relationship between two variables of interest depends on a third moderating variable (referred to as the moderator). The effect of the moderating variable is characterized statistically as an interaction that affects the relationship between the two other variables. In our case, we examined how SM1 GABA moderated significant behavioral effects observed in Model 3. We also included a potential moderating influence of SM1 GABA on the relationship between assessment and trial number, since trial number had a significant (but small) affect in Model 3. It is important to note that the ordering of the moderation analysis (i.e., causal relationship) was informed by the temporal structure of the experiment; experience of exertion and EV preceded participants' assessments of effort. If the interaction term of the regression is significant, the moderation of the relationship between EV and overassessments of effort is supported.

Results

Behavioral results

During the Assessment Phase, participants were able to exert and hold effort at the targeted levels (Fig. 3*A* shows exertion profiles from a representative participant). Participants' EV, calculated as the SD of exertion over the final 2 s of the hold period, increased with increasing levels of exertion (Fig. 3*B*; hierarchical linear model, $t = 7.42$, df = 1477, $\beta = 0.06$, $p = 1.93\text{e-}13$). Such increases in EV, with increasing motor output, are consistent with previous studies of isometric exertion which have reported that variability in force production increases in proportion to mean force exerted (i.e., signal dependent noise) (Semmler and Nordstrom, 1998; Enoka et al., 1999; Jones et al., 2002). We also found that participants' recalled assessments of effort were strongly correlated with levels of ME (Fig. 3*C*; hierarchical linear model, $t = 27.45$, df = 1477, $\beta = 0.95$, $p = 2.22\text{e-}134$), suggesting that participants developed a good understanding of the levels at which they were exerting.

To test our hypothesis regarding the relationship between EV and assessments of effort, we created a model that compared behavioral metrics related to exertion performance and participants' subjective assessments of effort. For each assessment trial, we calculated a measure of EVN as the SD of exertion divided by the ME level on that trial (i.e., the coefficient of variation). Normalizing EV by the ME level allowed us to control for the relationship between increasing levels of exertion and variability (Fig. 3*B*), so that we could evaluate how trial-to-trial variations in EV were related to assessments of effort. This model also included additional relevant factors that could influence EA: participants' ME in a trial, maximum exertion in a trial, and trial number. Trial number was included to model potential fatigue or training effects that could develop through repeated exertions. We found that individuals' EVN was related to the extent to which they reported exertions as being more effortful (Fig. 3*D*; hierarchical linear model, $t = 4.78$, df = 1474, $\beta = 0.25$, $p = 1.97\text{e-}06$). During trials in which participants exhibited increased EV, they had a more pronounced overassessment of effort. This is consistent with the idea that increased EV may be associated with an added cost that was related to participants' inflated assessments of effort. The only other factor that was significant in this model was trial number (Fig. 3*E*; hierarchical linear model, $t = 2.15$, df = 1474, $\beta = 0.11$, $p = 0.03$), which had a positive relationship with AE, suggesting that AE increased over the course of the experiment. However, this effect was very small compared with the effect of EV, consistent with EV having more of an influence on AEs. Notably, we independently replicated all these behavioral findings in a separate cohort of participants (see Fig. 4).

Relationships between behavior and sensorimotor GABA

To test our hypothesis that SM1 GABA modulates the relationship between EV and EA, we performed a between-participant regression of SM1 GABA levels and parameter estimates from the correlation between EVN and AE (represented in Fig. 3*D*). We found a significant correlation between SM1 GABA and the relationship between EV and over reporting of effort (Fig. 5*A*; Pearson's correlation, $n = 31$, $r = -0.56$ $p = 0.001$). In participants with lower SM1 GABA, EV increased overassessments of effort (Fig. 5*B*). Essentially, higher concentrations of SM1 GABA appear to have a protective effect that decreases the influence of EV on overassessments of effort.

To further explore the role of GABA on EV and subsequent EAs, we created a model which also included additional relevant factors that could influence EA: participants' ME in a trial, maximum exertion in a trial, trial number, SM1 GABA concentration, the interaction between SM1 GABA and EV, and the interaction between SM1 GABA and trial number (Fig. 5*C*). In this model, we again found significant effects of EV (hierarchical linear model, $t = 8.89$, df = 1471, $\beta = 0.43$, $p = 1.71\text{e-}18$) and trial number (hierarchical linear model, $t = 1.99$, df = 1471, $\beta = 0.11$, $p = 0.04$). We also found a significant interaction between SM1 GABA and EV, on EA (hierarchical linear model, $t = 3.12$, df = 1471, $\beta = -0.10$, $p = 0.002$). The structure of this model

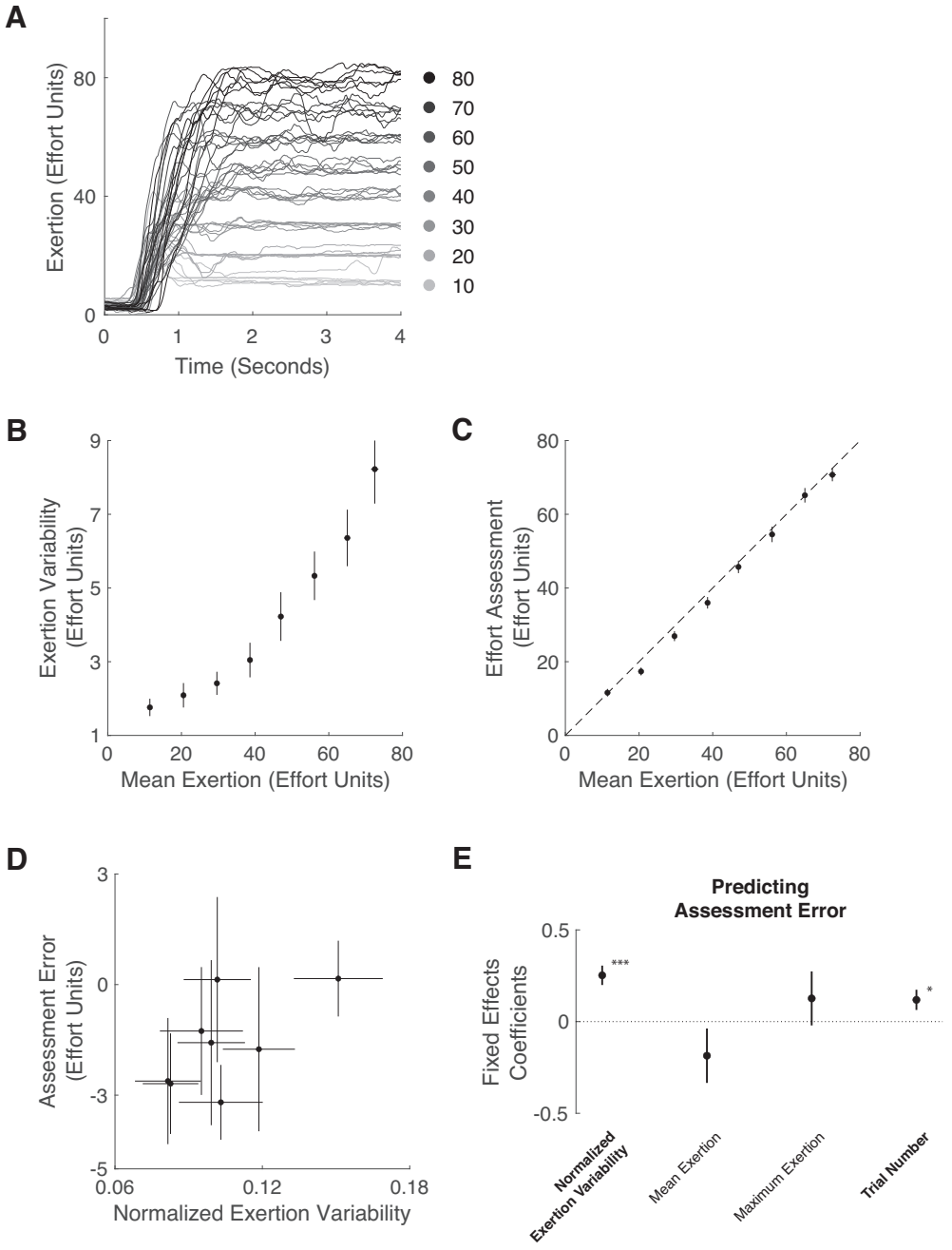

Figure 3. Behavioral results. ***A***, Exertion profiles, during the Assessment Phase, for an exemplar participant. Participants were able to quickly exert to the target level and hold for the duration of a trial. All exertion levels are presented in effort units, which are relative to participants' maximum exertion capacity. ***B***, EV as a function of ME during the Association Phase. EV and ME of each trial were calculated as the SD and average of the last 2 s of exertion output. For illustration purposes, EV and ME were pooled within target level and averaged across participants. Error bars indicate SEM. ***C***, EA as a function of ME during the Assessment Phase. Assessments of effort increased with participants' levels of ME, suggesting that participants had a good understanding of their levels of exertion. Dashed line indicates perfect agreement between assessments of effort and ME. For illustration purposes, EAs and ME were pooled within target level and averaged across participants. Error bars indicate SEM. ***D***, AEs increase with EVN. For each trial, an AE metric was calculated by taking the difference between the assessed effort and the ME. A EVN value was calculated by dividing EV by ME, which allowed performance during different levels of exertion to be evaluated in a unified model. For illustration, AEs and EVN were pooled within target level and averaged across participants. Error bars indicate SEM. ***E***, Shown are fixed effects coefficients from a hierarchal linear regression model predicting AE, for the following predictors: EVN, ME, maximum exertion, and trial number. Error bars indicate SEM. $^{***}p < 0.001$. $^{*}p < 0.05$.

assumed variability during exertion contributed to subsequent overassessments of effort, and that SM1 GABA levels moderated this relationship (Fig. 5*D*). This model shows that the amount of SM1 GABA had a significant moderating influence on the relationship between EV and errors in EA. Those participants who exhibited a lower SM1 GABA level had a stronger relationship between EV and subsequent overassessments of effort, whereas individuals who exhibited higher SM1 GABA showed a weaker relationship (Fig. 5*E*). We also considered the relationships between SM1 GABA and ME variability (Pearson's correlation, $n = 31$, $r = 0.14$, $p = 0.46$) and SM1 GABA and mean AE (Pearson's correlation, $n = 31$, $r = 0.04$, $p = 0.77$) to determine whether SM1 GABA level directly influenced motor performance or assessment accuracy. We failed to find significant relationships

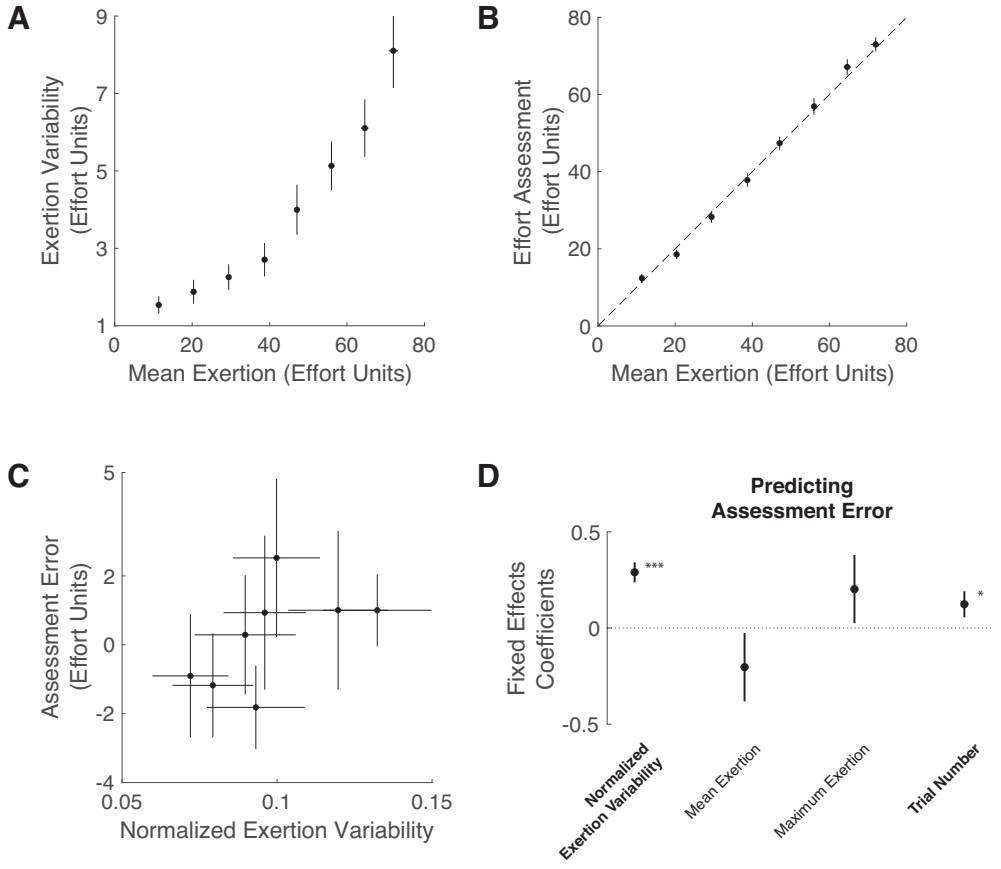

Figure 4. Replication of behavioral results. ***A***, EV as a function of ME during the Assessment Phase. This is an independent replication of the results in main Figure 3*B*, with data from prior experiments. EV and ME of each trial were calculated as the SD and average of the last 2 s of exertion output. As in Figure 3*B*, EV and ME were pooled within target level and averaged across participants. Error bars indicate SEM. As in the main experiment, statistical inference was conducted using the results from a hierarchal linear model. Participants' EV increased with increasing levels of exertion (hierarchal linear model, $t = 7.00$, df = 1870, $\beta = 0.06$, $p = 3.34e\text{-}12$). ***B***, EA as a function of ME during the Recall Phase. This is an independent replication of the results in main Figure 3*C* with data from prior experiments. Dashed line indicates perfect agreement between assessments of effort and ME. EAs and ME were pooled within target level and averaged across participants. Error bars indicate SEM. As in the main experiment, statistical inference was conducted using the results from a hierarchal linear model. Participants' EV increased with increasing levels of exertion (hierarchal linear model, $t = 30.28$, df = 1870, $\beta = 0.96$, $p = 2.96e\text{-}164$). ***C***, AEs increase with EVN. This is an independent replication of the results in main Figure 3*D* with data from a prior experiment. EVN and AE were calculated in the same manner as Figure 3*D*. AEs and EVN were pooled within target level and averaged across participants. Error bars indicate SEM. This analysis matches the primary behavioral results from the main text. As in the main experiment, statistical inference was performed using the results from a hierarchal linear model. Participants' EVN was related to the extent to which they reported exertions as being more effortful. ***D***, Shown are fixed effects coefficients from a hierarchal linear regression model predicting AE, for the following predictors: EVN, ME, maximum exertion, and trial number. Error bars indicate SEM. ***$p < 0.001$. *$p < 0.05$.

between these factors, suggesting that SM1 GABA best describes the relationship between EV and AE, rather than EV or AE alone.

To assess the discriminant validity of SM1 GABA, we also performed a Bayes factor analysis (Keysers et al., 2020; https://github.com/klabhub/bayesFactor), which provided strong evidence of the moderating role of SM1 GABA on the relationship between EVN and AE. We found moderate evidence against rIns GABA and OCC GABA influencing this relationship (Table 1).

Discussion

Here we show that variability in exertion is associated with inflations of EAs, making them feel more costly and that SM1 GABA levels are related to a decrease in the influence of EV on overassessments of effort. Our behavioral findings align with an established body of work showing that performance variability increases with increasing levels of exertion (Semmler and Nordstrom, 1998; Jones et al., 2002; Keysers et al., 2020) and decreases willingness to perform motor action (Salimpour and Shadmehr, 2014; Salimpour et al., 2015); and that increased SM1 GABA is related to improved perceptual acuity (Puts et al., 2011; Kolasinski et al., 2017). However, previous studies focused on fundamental aspects of motor performance, perception, and sensorimotor GABAergic function, and did not consider how such features influenced the higher-level cognitive function of subjective EA. Our results go beyond these studies by providing a framework by which motor performance influences feelings of effort and identifies a neurochemical mechanism that subserves this relationship.

Variability in motor output has been shown to both facilitate learning (Dhawale et al., 2019; Tumer and Brainard, 2007) and interfere with peak performance (Harris and Wolpert, 1998; Faisal et al., 2008). Notably, a recent study found that increased motor cortical noise served as an added cost that influenced individuals' decisions to perform a motor action (Salimpour and Shadmehr, 2014; Salimpour et al., 2015). Our data show that, in the context of physical exertion, variability acts as an added cost that inflates retrospective assessments of effort. This finding is consistent with EV having a deleterious effect on assessments of effort in which stable performance is advantageous. It is possible

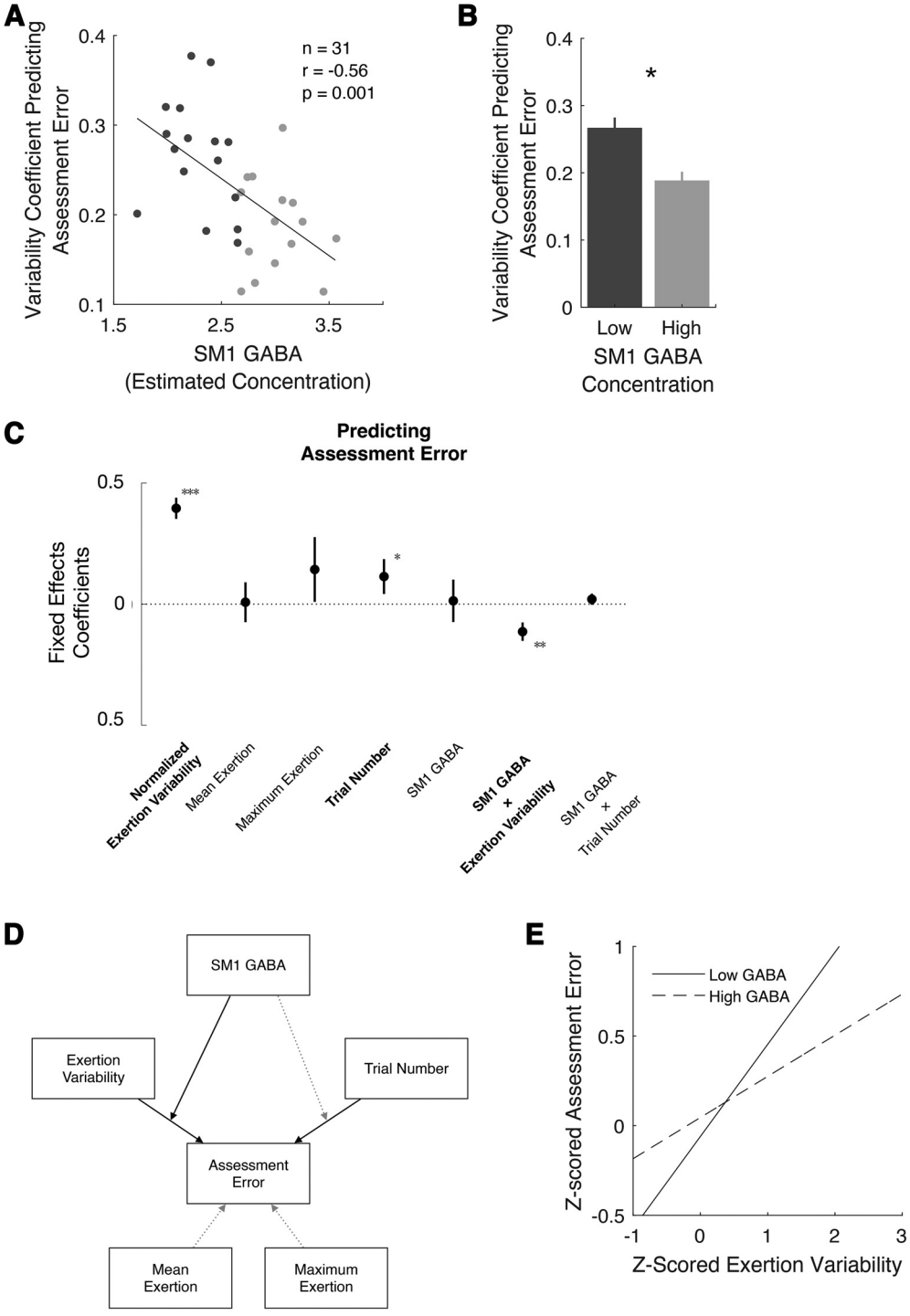

Figure 5. The influence of SM1 GABA on exertion and EA. ***A***, A between-participant regression considering the regression coefficient between perceptual errors and EVN as a covariate for SM1 GABA. As GABA concentration increases, the relationship between EVN and AE decreases. Participants are median split into a high GABA population (light gray circles) and a low GABA population (dark gray circles). ***B***, The regression coefficient between perceptual errors and EVN was significantly different for the high GABA and low GABA populations (unpaired t test, $t_{(28)} = -3.57$, $p = 0.0012$). ***C***, To fully assess the relationship between AE, EVN, and SM1 GABA concentration, we performed a hierarchal linear regression that included additional relevant factors. Shown are fixed effects coefficients from a hierarchal linear regression model predicting AE, for the following predictors: EVN, ME, maximum exertion, trial number, basal SM1 GABA concentration, the interaction between EVN and SM1 GABA concentration, and the interaction between trial number and SM1 GABA concentration. Error bars indicate SEM. $^{***}p < 0.001$. $^{**}p < 0.005$. $^{*}p < 0.05$. ***D***, We also created graphical representation of this model, and the moderating influence of SM1 GABA concentration on the relationship between EV and effort AEs. Black arrows indicate statistically significant effects. Gray arrows indicate effects that are not significant. ***E***, Illustrative plot of the moderating influence of SM1 GABA concentration on the relationship between EV and effort AEs. Lines indicate linear regressions between ME variability and AE. The lower SM1 GABA concentration, the stronger the relationship between the EV and over assessments of effort.

Table 1. Bayes factor analyses[a]

MRS ROI	*n*	*p*	Bayes factor
SM1	31	0.001	29.31
OCC	26	0.33	0.24
rIns	17	0.55	0.22

[a]Pearson correlation analysis in Figure 3*A* for all was replicated for all measured brain regions. The significance for the correlation is given with both a frequentist *p* value and a Bayes factor measure. The Bayes factor is interpreted as evidence against correlation ($BF \leq \frac{1}{3}$) or in support of a correlation ($10 < BF$).

that variability reduces an individual's certainty in the outcome of their motor performance, and this uncertainty may cause them to increase their ratings of effort.

Perceptual acuity for effort may be an important factor that influences assessments of effort. Weber's law is a long-standing theory in psychophysics that states that the just noticeable difference between perceptual stimuli increases with the stimulus intensity, and Weber's fraction is a measure that captures such perceptual acuity (Kacelnik and Brito e Abreu, 1998). It is possible that Weber's fraction for effort could be related to assessments of effort, such that individuals with greater perceptual acuity for effort could have smaller discrepancies between their EAs and their levels of exertion. Given GABA's role in perceptual acuity (Puts et al., 2011; Kolasinski et al., 2017), it could be a factor that modulates effort perceptions and assessments. While we did not measure participants' Weber fraction for effort, the study of EA using traditional psychophysical approaches could be important to understanding judgments of effort and effort-based decision-making in the future.

Studies of economic valuation use the mean-variance framework to represent the utility of an option as its outcome value penalized by the degree of outcome uncertainty (i.e., risk) (D'Acremont and Bossaerts, 2008). In this framework, outcome uncertainty acts as an added cost that lowers the overall utility of an option. In the context of effort-based valuation, performance variability may lead to uncertainty in understanding the outcome of exertion, which could inflate the cost of effort in an analogous fashion. While we did not directly examine valuations of effort in this study, in the future it will be interesting to examine whether such mean-variance representations of risk (in which variance is captured by EV) are related to prospective effort-based decision-making.

Our experimental data and GABA measurements allowed us to distinguish how SM1 GABA levels were related to effortful exertion and assessments of effort, and the link between exertions and assessments. We found that SM1 GABA was related to the relationship between variability and EAs. These results are consistent with studies of sensorimotor discrimination which found that individuals with better tactile perception had higher basal SM1 GABA concentrations (Puts et al., 2011; Kolasinski et al., 2017). Across several different cognitive tasks, and their associated brain regions, increased GABA levels have been associated with improved performance (Boy et al., 2010; Sumner et al., 2010; Jocham et al., 2012). From these works, it has been suggested that GABA facilitates tuning of cortical activity, modulating surround inhibition, to allow for more precise behavioral performance. While we did not directly measure perceptual acuity of effort, and strictly focused on EAs, it is possible that SM1 GABA may influence the acuity of effort perception which feeds into assessments of effort.

Our results suggest that, rather than SM1 influencing motor performance or EA alone, SM1 GABA modulates the transformation from motor performance to eventual EAs. Assessments of effort likely rely on comparisons between immediate feelings of exertion and prior sensorimotor representations of exertion. GABA could facilitate these comparisons by sharpening prior representations of exertion, and making them more salient, thus allowing for increased acuity in EA. This aligns with the body of work relating SM1 GABA levels to motor performance (Stagg et al., 2011; Kolasinski et al., 2019). It is also possible that GABA's influence could occur at that level of the sensorimotor comparison itself, ensuring more precise computations between prior representations of effort and immediate exertion. This is consistent with studies implicating SM1 GABA in tactile perceptual acuity (Puts et al., 2011; Kolasinski et al., 2017). Our study points to an interaction between the effects of GABA on exertion performance and EA. Future works will be needed to explore how GABA may separately influence such sensorimotor and perceptual integration.

It is important to note that our SM1 GABA voxel placement encompassed aspects of both the primary motor cortex and primary somatosensory cortex, so we were unable to discriminate their distinct contributions. Notably, SM1 GABAergic function has been associated with voluntary suppression of unwanted behavior (Coxon et al., 2006; van den Wildenberg et al., 2010), and it is possible that SM1 GABA inhibits the influence of performance variability on EA. While our results are most consistent with the reports of associations between sensory function and GABA, it will be important to distinguish the function of motor cortical and somatosensory GABA to EAs in the future.

Recently, it has been suggested that discrepancies between an individual's perceptions of their ability and actual sensorimotor capacity are related to their assessments of effort and feelings of fatigue (Stephan et al., 2016; Kuppuswamy, 2017; van der Schaaf et al., 2018). Essentially, individuals with a more accurate interoceptive sense may be better able to judge their bodily state and appropriately tune their nervous system to accommodate their desired sensorimotor output. In the context of the effort exertions and assessments in our experiment, such an interoceptive awareness may be critical for judgments of how EV contributes to motor output and assessments of effort.

Our experiments were designed to study EA in a well-controlled environment; and as a result, our task was not as naturalistic as the EAs made during daily life. This raises the question of how our findings might translate to more ecologically valid settings. Several studies of motor control and ergonomics have observed that increased physical fatigue is associated with increased motor variability during arm movements (Gates and Dingwell, 2011), leg movements (Cortes et al., 2014), cycling (Kuipers et al., 1985), and even manual assembly line work (Srinivasan and Mathiassen, 2012). Individuals reported higher perceived exertion while in a state of fatigue and exhibited more variability in their motor performance. In the future, it will be important to investigate whether well-controlled measures of exertion performance and EA, and their relationship with basal SM1 GABA levels, are related to performance in real-world tasks. These relationships could provide markers for predicting individuals' assessments of effort, which inform pharmacological or noninvasive brain stimulation montages that act on the GABAergic system to enhance willingness to exert.

In conclusion, our study provides evidence that the brain's neurochemical composition facilitates how physical exertions are transformed into accurate assessments of effort. The present work implicates a mechanism by which variability in motor performance inflates assessments of effort, and GABA in the SM1 dampens the influence of EV on these overassessments. These results suggest that GABA in the SM1 moderates the integration

of EV into EA. The present work begins to bridge the gap in understanding how basic sensorimotor function influences higher-level assessments of effort, which to date has remained poorly characterized. Moreover, from a clinical standpoint, the formation of assessments of effort is likely to prove important in understanding feelings of amotivation and fatigue (Stephan et al., 2016; Kuppuswamy, 2017; van der Schaaf et al., 2018). From this perspective, the behavioral and neural underpinnings of EA provide a foundation for the development of interventions aimed at optimizing effortful exertion.

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