Trial-by-trial neural variability is an individual human trait

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Abstract

A wide variety of sensory studies have shown that cortical neural activity varies dramatically across trials. This trial-by-trial neural variability is relatively large in the pre-stimulus period and considerably smaller (quenched) following stimulus presentation. The magnitude of neural variability affects behavior such that perceptual performance is better on trials and in individuals where variability quenching is larger. Are neural variability magnitudes transient states that change with time, attentional demands, and/or cognitive requirements? Or are they static individual traits? Here, we show that neural variability magnitudes are remarkably consistent across four different tasks with different attentional and cognitive demands as well as across experimental sessions separated by one year. These results reveal that, in adults, neural variability magnitudes are solidified individual traits, which change little with behavioral state or time, and may predispose individual subjects to exhibit distinct behavioral capabilities.

Significance statement

Brain activity varies dramatically from one moment to the next. Recent research has revealed that differences in the magnitude of trial-by-trial neural variability can explain differences in behavioral performance across subjects. Do neural variability magnitudes represent flexible states that are under the control of an individual or are they static individual traits? By comparing neural variability magnitudes across four different experiments with different attentional and cognitive demands, and across two experimental sessions separated by one year, we demonstrate that

neural variability magnitudes are remarkably consistent individual traits. We suggest that the magnitude of neural variability may predispose individual subjects to exhibit different behavioral capabilities.

Introduction

Neural activity in the mammalian brain is notoriously variable/noisy over time (Vreeswijk and Sompolinsky, 1996; Faisal et al., 2008). This variability is apparent across trials before the presentation of a stimulus (i.e., ongoing variability) and also after the presentation of a stimulus (i.e., stimulus-evoked variability) (Arieli et al., 1996; Churchland et al., 2010; Goris et al., 2014). Recent research has shown that ongoing neural variability is considerably larger than stimulus-evoked variability, thereby demonstrating that sensory stimulation reduces ("quenches") ongoing neural variability (Churchland et al., 2010). Such variability quenching was reported consistently across studies examining a variety of cortical areas and arousal states, while using different types of stimuli, and when measuring neural activity with electrophysiology in animals (Monier et al., 2003; Finn et al., 2007; Mitchell et al., 2007; Churchland et al., 2010, 2011; Hussar and Pasternak, 2010) or neuroimaging in humans (He, 2013; He and Zempel, 2013; Schurger et al., 2015).

Several lines of evidence show that neural variability has a strong impact on behavioral performance. First, larger variability quenching is associated with better perceptual performance, whether examined across trials (Schurger et al., 2015) or across individual subjects (Arazi et al., 2017). Second, actively allocating attention to a visual stimulus improves behavioral performance primarily by reducing the trial-by-

trial response variability of single neurons (Mitchell et al., 2007) and the shared/correlated variability across the local neural population (Cohen and Maunsell, 2009; Mitchell et al., 2009). Third, increasing dopamine and norepinephrine levels increases the magnitude of neural variability in both humans (Garrett et al., 2015) and animals (Aston-Jones and Cohen, 2005; Sakata et al., 2008) and generates behavior that is more exploratory (variable) (Aston-Jones and Cohen, 2005).

While neural variability is under the flexible control of attention and neuromodulation to a certain extent, many of the mechanisms that generate and govern neural variability are likely to be a product of individual genetics and early development. For example, mechanisms that govern the reproducibility of neural activity by maintaining stable excitation-inhibition balances (Turrigiano, 2011) and reliable synaptic transmission (Ribrault et al., 2011), are the product of individual genetics and environmental exposure during early critical periods (Hensch, 2005; Takesian and Hensch, 2013). Since individual subjects have different genetics and experience different environments, one may expect intrinsic neural variability magnitudes to differ across individuals and potentially predispose them to different behavioral capabilities.

To determine whether neural variability magnitudes of individual adult subjects are flexible or static, we measured neural variability with EEG while subjects performed four tasks that differed in their structure, stimulus, attentional demands, and cognitive requirements. These experiments allowed us to quantify neural variability across trials where the subjects' attention was either diverted away from the

stimulus (to an unrelated task) or focused on the stimulus using tasks with varying cognitive requirements. The same subjects performed all four experiments in two experimental sessions separated by a year. This experimental design enabled us to quantify individual neural variability magnitudes in each of the experiments and experimental sessions. By examining the consistency of individual neural variability magnitudes across experiments and over time, we determined whether these measures reflect flexible states or static individual traits.

Materials and Methods

Subjects. Twenty-four subjects (eight males, mean age during the first session= 23.7 years, SD= 1.4) took part in this study. All subjects had normal or corrected-to-normal vision. The study was approved by the Ben-Gurion University Internal Review Board. Subjects provided written informed consent during both experimental sessions and were either paid for their participation or received research credit.

Experimental design. All subjects completed four experiments in each of the two experimental sessions. The gap in time between the first and the second session was 12.3 months on average (SD = 1.1). The study was performed in a dark and sound proof room. The stimuli were presented using MATLAB (Mathworks, Inc., USA) and Psychtoolbox (Brainard, 1997).

Checkerboard experiment: The visual stimulus consisted of a checkerboard annulus with an inner radius of 0.6° visual angle and an outer radius of 3.7° visual angle. The experiment contained 600 trials: 400 trials with the stimulus and 200 trials where the stimulus was omitted. The stimulus was presented for 50ms and followed by a

randomized inter-trial interval lasting 750-1200ms. The experiment also included an orthogonal color-detection task at fixation, which was intended to divert attention away from the checkerboard stimulus. Subjects were instructed to press a key whenever the black fixation cross changed its color to gray. The experiment contained 80 random color changes, which lasted 30ms and subjects had one second to respond. Correct and incorrect responses were indicated by changing the fixation cross to green or red, respectively.

Choice reaction time (CRT) experiment: A black triangle or a circle was presented at the center of the screen for 300ms on each trial. Subjects were instructed to press the right or left arrow keys, respectively, as quickly as possible using their right index finger. Each trial was followed by an inter-trial interval of 1200ms. A total of 200 trials were presented, 100 trials with each of the two stimuli.

Go-no-go experiment: Stimuli and structure were identical to those described in the CRT experiment, except that participants were instructed to press the spacebar as quickly as possible with their right index finger whenever they saw a circle (“go” trial) and not when the triangle was presented (“no go” trial). A total of 300 trials were presented and 80% of the trials contained the “go” stimulus.

2-back experiment: Stimuli were composed of 4 Chinese letters, presented at the center of the screen and participants were asked to press the "J" key whenever the current letter matched the one that was presented 2 trials before. Each letter was presented for 500ms and followed by an inter-trial interval of 500ms. A total of 300 trials were presented with 20% of them containing a 2-back repeat.

EEG and eye tracking recordings. EEG data were recorded using a 64-channel BioSemi system (Biosemi Inc., Netherlands), connected to a standard EEG cap according to the international 10-20 system. Data were referenced to the vertex electrodes. Electrooculography (EOG) was recorded using two electrodes at the outer canthi of the left and right eyes and one electrode placed below the right eye. In the checkerboard experiment, the position of the right eye was recorded using an eye-tracker (EyeLink 1000, SR-research) at a sampling rate of 1000Hz.

EEG preprocessing. Data was analyzed using Matlab (Mathworks, Inc.) and the EEGLAB toolbox (Delorme and Makeig, 2004). Continuous EEG data was down sampled to 512Hz, filtered using a 1-40 Hz band pass filter, and re-referenced to the bilateral mastoid electrodes. EEG epochs were extracted using a time window of 700ms (200ms pre-stimulus to 500ms post-stimulus) and baseline correction was not performed so as not to alter trial-by-trial variability in the pre-stimulus interval. In the checkerboard experiment only trials where stimulus was presented were extracted, in the CRT experiment trials with both stimuli (circle or triangle) were extracted, in the go-no-go experiment only the “go” trials were extracted and in the 2-back experiment trials with the four different stimuli (Chinese letters) were extracted. Epochs containing absolute amplitudes that exceeded 70μV or where the power exceeded 25db in the 20-40Hz frequency range were identified as containing eye blinks or muscle artifacts, respectively, and were removed from further analysis. In the checkerboard experiment identification of eye blinks was confirmed by eye tracking; trials containing horizontal or vertical eye movements that exceeded 1.5 SD of the mean were identified as trials where fixation was not maintained (i.e. trials containing saccades) and excluded from EEG analyses. Mean number of trials across

subjects and sessions after trials rejection in the four experiment was 249 trials in the checkerboard experiment (SD=50), 146 trials in the CRT experiment (SD=39), 161 trials in the go-no-go experiment (SD=53), and 254 trials in the 2-back experiment (SD=46). The mean number of trials did not differ between the first and second experimental sessions.

EEG data analysis. Trial by trial variability was computed for each time-point in the extracted epochs (-200 to 500ms) for each of the 64 electrodes, in each subject separately. Trials from the first and second sessions were analyzed separately. Absolute level of trial-by-trial variability in the pre-stimulus interval was computed as the mean variance within a time window of -200ms and 0ms pre-stimulus. Absolute level of trial-by-trial variability in the post-stimulus interval was computed as the mean variance within a time window of 150-400ms post-stimulus.

Relative trial-by-trial variability was computed by converting the variability time courses to percent change units relative to the mean trial-by-trial variability in the pre-stimulus period (-200 to 0ms). We then estimated variability quenching for each subject in each task and session by computing the difference in variability between the pre-stimulus period (-200 to 0ms) and post stimulus period (150 to 400ms). We focused our analyses on the four occipital electrodes (O1, O2, PO7 and PO8) with the strongest visual responses.

To ensure that changes in variability were not driven by changes in the mean EEG activity, we computed the coefficient of variation (CV) by dividing the magnitude of variability by the area under the curve of the mean ERP response (i.e., the ERP amplitude). This was computed separately for the pre (-200 to 0ms) or post (150 to

400ms) stimulus intervals. We then computed CV quenching as the relative change in the CV between the pre and post stimulus periods (in units of percent change). To examine the temporal dynamics of the CV, we computed it in the same manner, while using a sliding window with a width of 50ms and overlap of 5ms (Figure 7).

Behavioral data analysis. Mean accuracy, mean reaction time (RT) and reaction time variability (across trials) was computed for each subject and each session, in CRT, go-no-go and two-back tasks as well as the color-detection task in the checkerboard experiment. The first 10 trials in each experiment and trials with RT below 200ms were excluded from the analysis. Trials with incorrect responses were excluded from the RT analyses.

Statistical Analysis. We assessed relationships across measures using Pearson's correlations. The statistical significance of the correlation coefficients was assessed with a randomization test where we shuffled the labels of the subjects before computing the correlation coefficient. This procedure was performed 10,000 times while shuffling the labels across subjects randomly each time to generate a null distribution for each pair of EEG/behavioral measures. For the true correlation coefficient to be considered significant it had to be higher than the 95th percentile or lower than the 5th percentile of this null distribution (i.e., equivalent to a p-value of 0.05 in a one tailed t-test). Comparisons across experiments/tasks were performed using a one-way ANOVA with task as the only factor, followed by post hoc Tukey's tests when the initial result indicated significant differences.

Electrode offset variability. The Biosemi EEG system utilizes active electrodes, which do not yield a measure of impedance. Instead, fluctuations in electrode offset (i.e.

slow changes in the voltage potential over time) are considered the best indication for the quality of EEG recording (Kappenman and Luck, 2010). We, therefore, computed the electrode offset variability across trials for each subject during each of the experiments in each experimental session. We computed the offset value for each trial, the variability across trials in each of the four examined electrodes, and finally the mean across electrodes in each experiment. We then correlated offset variability with the EEG variability measures to check if differences in the quality of EEG recordings across individuals could explain our results.

Gaze variability. Gaze position was measured during the checkerboard experiment only. We computed the distance from the fixation cross at each time point from stimulus onset to 500ms post stimulus, then computed the standard deviation across trials for each time point, and finally averaged across all time points (0-500ms) to generate a single measure of gaze variability per subject. We correlated gaze variability across the first and second sessions to determine whether individual subjects exhibited reproducible gaze variability across sessions. Three subjects were excluded from this analysis due to difficulties in the calibration process of the eye tracker in one of sessions.

Results

Twenty-four subjects completed two experimental sessions separated by one year. Each session included four experiments that differed in their structure, stimulus, attentional demands, and cognitive loads. In the first experiment, subjects passively observed a checkerboard annulus on each trial, while their task was to identify and

report infrequent color changes of the fixation cross. This enabled us to measure neural variability magnitudes to an un-attended stimulus (i.e., the checkerboard). In the second experiment, subjects performed a choice reaction time (CRT) task where they responded with one button to a circle stimulus and with another button to a triangle stimulus. This enabled us to measure neural variability magnitudes to an attended stimulus during a very easy task. In the third experiment, subjects performed a go-no-go task where they responded only to the circles (go trials) and not to the triangles (no-go trials). This enabled us to measure neural variability magnitudes to an attended stimulus during a somewhat harder task that required response inhibition. In the final experiment, subjects performed a 2-back task where they were presented with alternating Chinese letters and instructed to respond whenever the current letter matched the letter that was presented two trials before. This enabled us to measure neural variability magnitudes to an attended stimulus during a difficult working memory task.

Differences in the attentional and cognitive demands of the four tasks were clearly evident in the behavioral performance of the subjects (Figure 1). One way ANOVA analyses demonstrated that there were clear differences in the accuracy rates ($F_{(3,92)} = 99.1,\ p =. 1x10^{-27}$), mean reaction times ($F_{(3,92)} = 56.7,\ p =. 8x10^{-20}$), and reaction time variability ($F_{(3,92)} = 131.9\ ,\ p =. 3x10^{-31}$) across the four tasks. Post-hoc Tukey's tests revealed that there were significant differences across all pairs of tasks ($p < 0.01$ for all behavioral measures), except for the CRT and Go-no-go tasks. Specifically, accuracy rates were higher, mean reaction times were lower, and reaction time variability was lower in the CRT and Go-no-go tasks as compared with the color-detection task in the Checkerboard experiment and the 2-back task. In

addition, accuracy rates were significantly higher, mean reaction times were lower, and reaction time variability was lower in the color-detection task as compared with the 2-back task. This demonstrates that the CRT and Go-no-go tasks were easier than the color-detection and 2-back tasks and that the 2-back task was harder than the color-detection task.

Note that in the Checkerboard experiment the relatively difficult color-detection task diverted the subjects' attention away from the checkerboard stimulus, thereby allowing us to quantify trial-by-trial neural variability to an unattended stimulus. In contrast, the 2-back task required that subjects attend the stimulus, thereby allowing us to quantify trial-by-trial neural variability to a strongly attended stimulus.

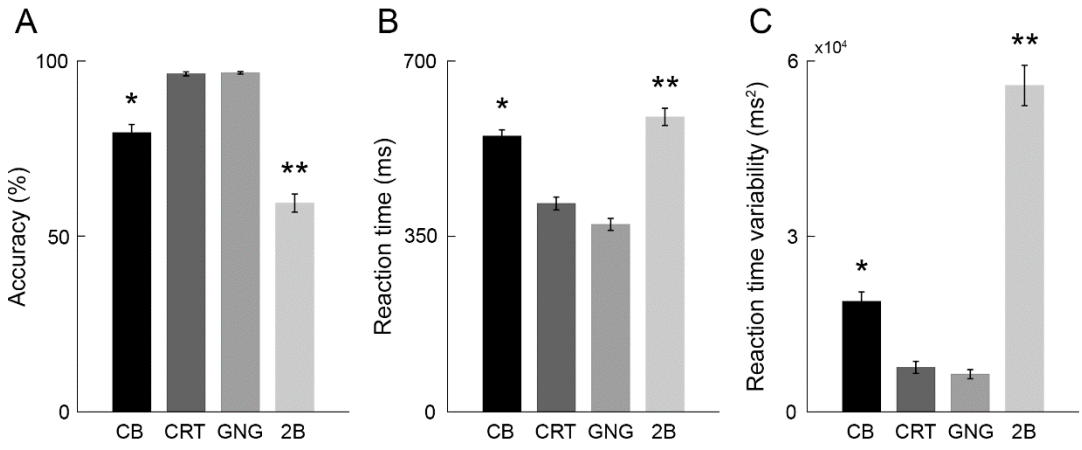

Figure 1: Behavioral performance measures. Mean across subjects and sessions for accuracy (A), reaction time (B) and reaction time variability (C) in each of the four tasks. Error bars: standard error of the mean across subjects. Asterisks: Significant differences across experiments (Post-hoc Tukey's tests, $p < 0.01$). One asterisk: Significant differences between CB experiment and CRT or GNG experiments. Two asterisks: Significant differences

between 2B experiment and all other experiments. CB: checkerboard, CRT: choice reaction time, GNG: go-no-go, 2B: 2-back.

Neural variability quenching

We examined trial-by-trial neural variability as a function of time before and after stimulus presentation in each of the four experiments (Figure 2). Trial-by-trial variability was reduced (i.e., quenched) following stimulus presentation in all experiments and in both recording sessions performed a year apart. Variability quenching was sustained from 150 to 400ms after stimulus presentation and most evident in occipital electrodes (O1, O2, PO7 and PO8). We quantified variability quenching as the relative change (in units of percent change) between pre-stimulus (-200 to 0ms) and post-stimulus (150 to 400ms) periods, while focusing our analyses on the four electrodes noted above.

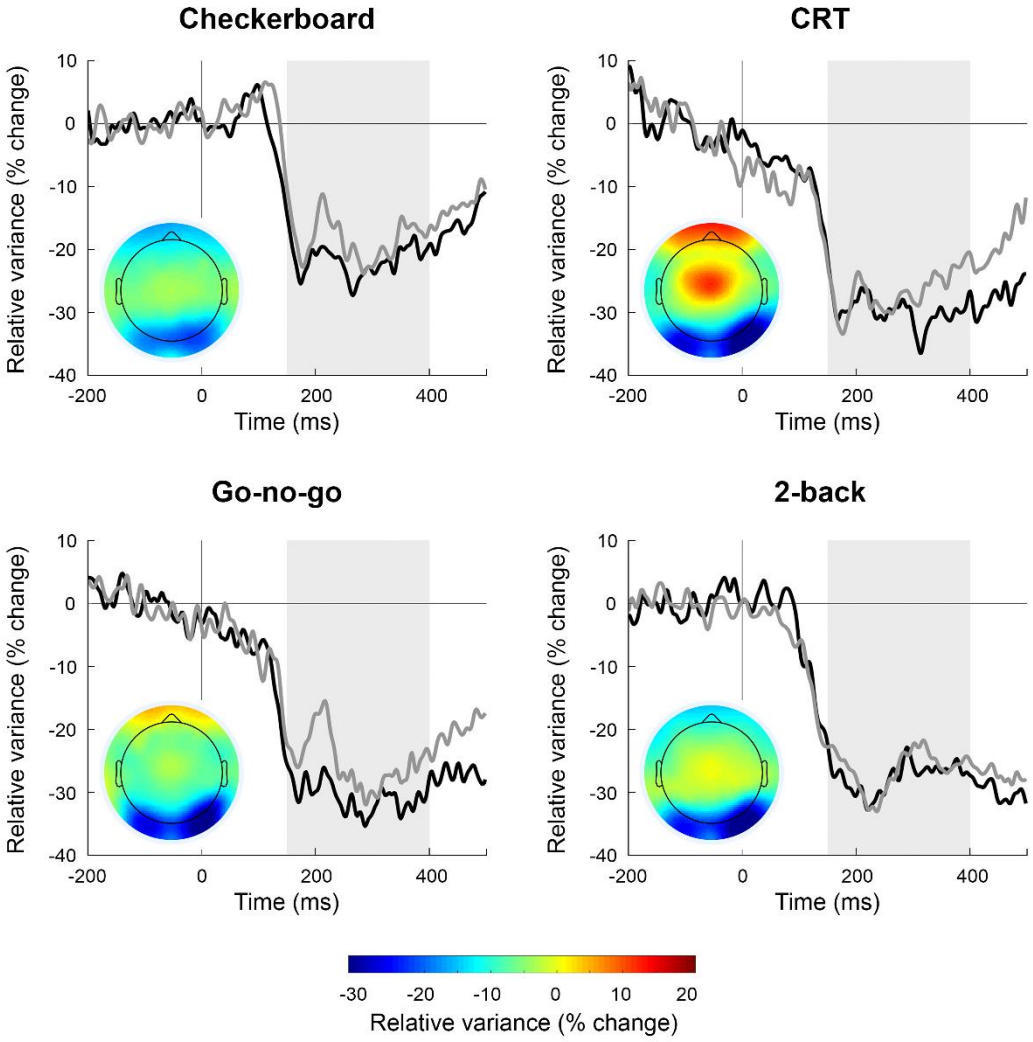

Figure 2: Temporal and spatial dynamics of trial-by-trial neural variability. Each time-course represents the changes in relative trial-by-trial variability (percent-change units relative to the pre-stimulus period) during the first (black) or second (grey) experimental session, which were separated by one year. Each panel displays the results of a different experiment. Gray background: 150-400ms post-stimulus period with sustained variability quenching that was selected for further analyses. Insets: topographic maps of variability quenching magnitudes during the 150-400ms window, demonstrating that quenching was strongest in occipital electrodes across all four experiments.

Neural variability is a stable individual trait

We quantified three measures of trial-by-trial variability for each subject. Absolute trial-by-trial variability was quantified in the pre-stimulus (-200 to 0ms) and post-stimulus (150-400ms) periods for each subject, in each of the four experiments, and each of the experimental sessions (see Materials and Methods). Variability quenching was quantified as the difference between variability magnitudes in the pre and post stimulus periods. All three measures of variability were strongly and significantly correlated across the two EEG recording sessions in each of the four experiments ($r(24) > 0.58, p < 0.003$, Figure 3). This demonstrates that the neural variability magnitudes of individual subjects barely changed over a one year period.

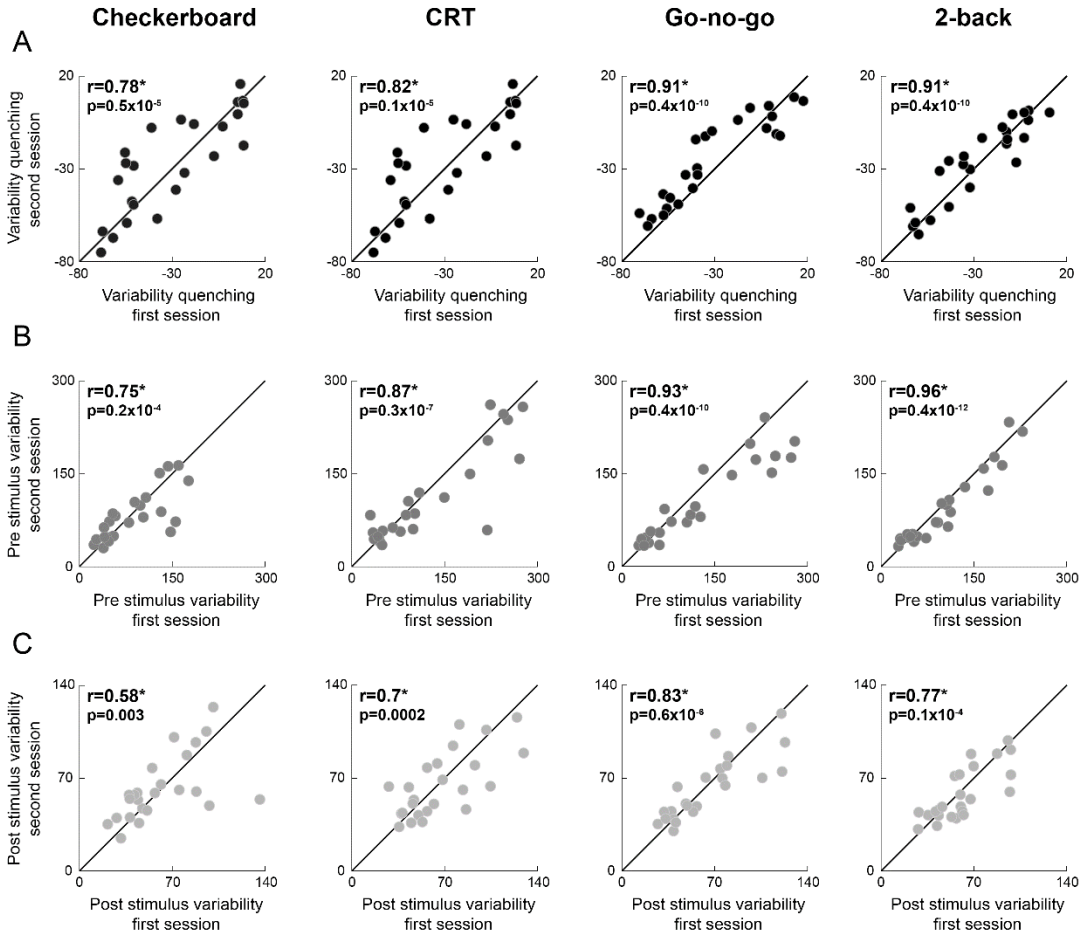

Figure 3: Individual neural variability magnitudes were consistent across experimental sessions separated by one year. Scatter plots present the magnitudes of variability quenching (A), pre-stimulus variability (B), and post-stimulus variability (C) in individual subjects during the first and second experimental sessions for each of the four experiments. The unity line is drawn for reference in each panel. Each point represents a single subject. Asterisks: significant correlation as assessed by a randomization test ($p < 0.003$). Pearson's correlation coefficients and p-values are noted in each panel.

Individual variability magnitudes were also strongly correlated across experiments. Given the strong correlations across sessions (Figure 3), we averaged each of the variability measures across the two sessions. We then compared individual variability magnitudes across experiment pairs. This analysis revealed strong, positive, and significant correlations across all pairs of experiments when examining variability quenching ($r(24) > 0.74, p < 0.4x10^{-4}$, Figure 4), pre-stimulus variability ($r(24) > 0.85,\ p < 0.8x10^{-7}$, Table 1), or post-stimulus variability ($r(24) > 0.89, p = 0.4x10^{-8}$, Table 1) magnitudes.

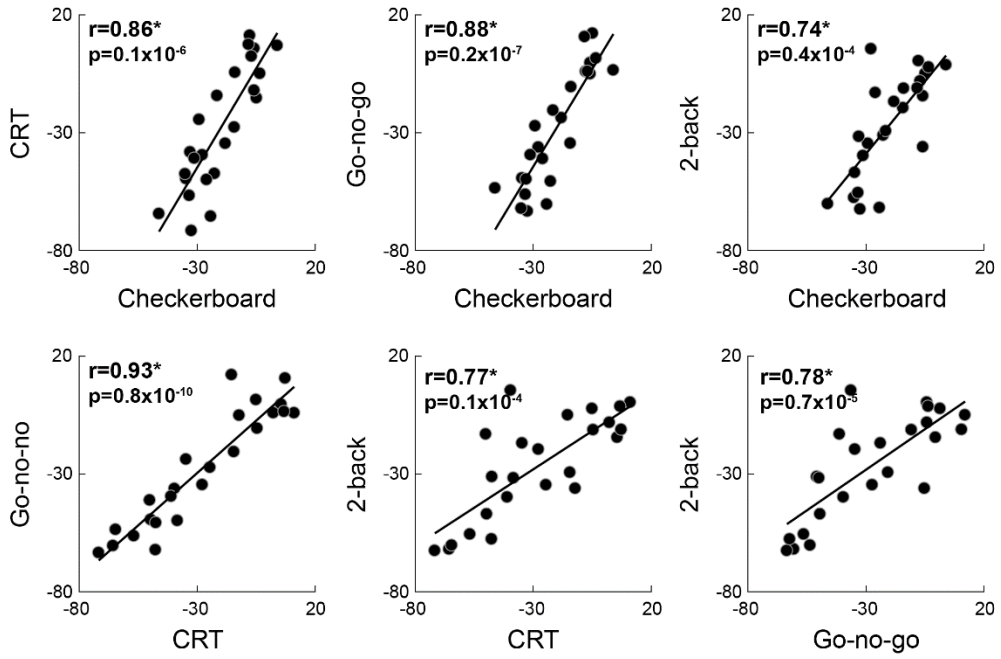

Figure 4: Individual variability quenching magnitudes were consistent across experiments. Scatter plots demonstrate the relationship between variability quenching magnitudes in each pair of experiments. Each dot represents a single subject. The linear fit is drawn for reference in each panel. Asterisks: significant correlation as assessed by a randomization test ($p < 0.0004$). Pearson's correlation coefficients are noted in each panel.

	CB-CRT	CB-GNG	CB-2B	CRT-GNG	CRT-2B	GNG-2B
Pre stimulus	r = 0.86 p = $0.5*10^{-7}$	r =0.93 p = $0.8*10^{-10}$	r = 0.86 p = $0.7*10^{-7}$	r = 0.96 p = $0.3*10^{-10}$	r = 0.89 P=$0.6*10^{-8}$	r = 0.93 p = $0.8*10^{-10}$
Post stimulus	r = 0.9 p = $0.1*10^{-8}$	r=0.9 p = $0.2*10^{-8}$	r = 0.89 p = $0.3*10^{-8}$	r = 0.95 p = $0.1*10^{-11}$	r = 0.9 p = $0.1*10^{-8}$	r = 0.94 p = $0.1*10^{-10}$

Table 1: individual magnitudes of pre-stimulus (top row) and post-stimulus (bottom row) neural variability were strongly correlated across experiments. Pearson's correlation coefficients and p-values (as assessed by a randomization test) are noted for each pair of experiments. CB: checkerboard, CRT: choice reaction time, GNG: go-no-go, 2B: 2-back.

Differences in neural variability across tasks

As demonstrated above, the four tasks examined in this study included different visual stimuli and imposed different cognitive and attentional demands (Figure 1). Since previous research suggests that neural variability should decrease with attentional load, we compared both variability quenching and absolute variability in the pre and post stimulus periods across the four tasks (Figure 5). While variability quenching was somewhat larger in the three experiments where the stimulus was attended (i.e., CRT, Go-no-go, and 2-back) as compared with the experiment where the stimulus was not (i.e., the checkerboard experiment), these differences were not statistically significant ($F_{(3,92)} = 0.74,\ p = 0.53$, one way ANOVA). Neural variability in the pre-stimulus and post-stimulus periods were also not significantly different across tasks ($F_{(3,92)} = 1.49,\ p = 0.22;\ F_{(3,92)} = 0.44, p = 0.72$; respectively, one way ANOVA).

Most importantly, differences in neural variability magnitudes across subjects were considerably larger than differences across tasks. To demonstrate this, we computed the mean pair-wise differences in variability across subjects (within each task) and the mean pair-wise differences in variability across tasks. Between-subject differences in neural variability magnitudes were significantly larger than between-task differences in neural variability magnitudes when comparing pre-stimulus variability (two tailed t-test, $p = 0.008$), post-stimulus variability (two tailed t-test , $p = 0.5x10^{-5}$), and variability quenching (two tailed t-test , $p = 0.2x10^{-6}$).

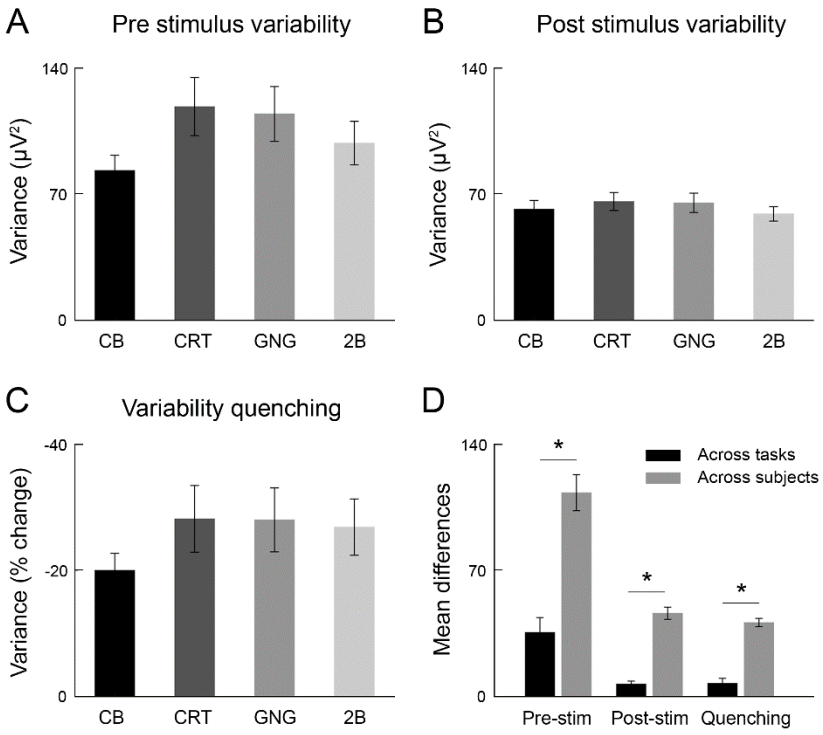

Figure 5: Neural variability differences across experiments. (A) Neural variability quenching. (B) Neural variability in the pre-stimulus interval (-200 to 0ms). (C) Neural variability in the post-stimulus interval (150 to 400ms). (D) Mean differences in the magnitudes of neural variability across tasks (black bars) and across subjects (gray bars). Error bars: Standard error of the mean across subjects. CB: checkerboard, CRT: choice reaction time, GNG: go-no-go, 2B: 2-back. Asterisks: significant differences (two tailed t-test, $p < 0.001$).

Neural variability and behavioral performance

We found significant relationships between individual neural variability magnitudes and accuracy rates in the 2-back working memory experiment (Figure 6A). Accuracy rates were positively correlated with pre-stimulus variability magnitudes ($r(24) = 0.45, p = 0.025$; uncorrected) and post-stimulus variability magnitudes ($r(24) =$

$0.44, p = 0.033$; uncorrected). Accuracy rates were also negatively correlated with variability quenching magnitudes ($r(24) = -0.4, p = 0.049$; uncorrected). Note that variability quenching magnitudes are negative such that larger (more negative) quenching was associated with better accuracy. Taken together, these results suggest that individuals with larger pre-stimulus variability who quench more, exhibit better cognitive performance.

All other correlations between neural variability magnitudes and behavioral performance measures (i.e., accuracy, mean reaction time, and reaction time variability) were not significant (Figure 6 & Table 2). Note that the 2-back task was the hardest task in our study with a mean accuracy rate of 60% across subjects (Figure 1).

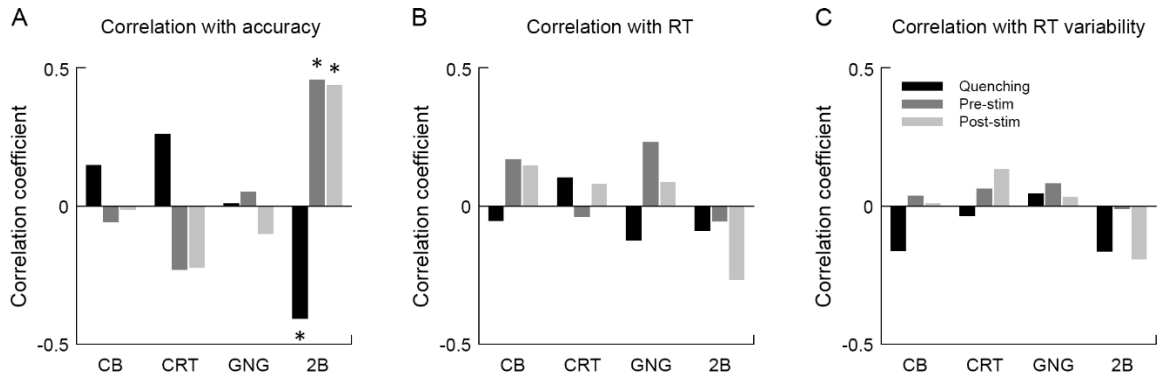

Figure 6: Relationships between neural variability and behavior. Pearson's correlation coefficients were calculated between each of the three behavioral measures: accuracy (A), mean RT (B), RT variability (C) and each of the three variability measures: variability quenching (black bars), pre stimulus variability (dark gray bars) and post stimulus variability (light gray bars). Asterisks indicate significant correlations as assessed by a randomization analysis ($p < 0.05$, uncorrected). CB: checkerboard, CRT: choice reaction time, GNG: go-no-go, 2B: 2-back.

	Accuracy			Mean RT			RT variability		
	Quench	**Pre**	**Post**	**Quench**	**Pre**	**post**	**Quench**	**Pre**	**Post**
CB	r=0.14 p=0.49	r=-0.07 p=0.79	r=-0.01 p=0.96	r=-0.05 p=0.81	r=0.18 p=0.43	r=0.14 p=0.5	r=-0.16 p=0.45	r=0.04 p=0.87	r=0 p=0.97
CRT	r=0.26 p=0.22	r=-0.23 p=0.28	r=-0.22 p=0.3	r=0.1 p=0.63	r=-0.04 p=0.86	r=0.08 p=0.71	r=-0.03 p=0.87	r=0.06 p=0.77	r=0.13 p=0.54
GNG	r=0 p=0.97	r=0.05 p=0.81	r=-0.1 p=0.64	r=-0.12 p=0.57	r=0.23 p=0.28	r=0.09 p=0.69	r=0.04 p=0.84	r=0.08 p=0.71	r=0.03 p=0.88
2B	r=-0.4* p=0.049	r=0.45* p=0.025	r=0.44* p=0.033	r=-0.09 p=0.68	r=-0.05 p=0.8	r=-0.26 p=0.21	r=-0.16 p=0.45	r=0 p=0.97	r=-0.19 p=0.37

Table 2: Relationship between measures of neural variability and behavioral measures. Pearson's correlation coefficients and p-values for each behavioral (accuracy, mean RT or RT variability) and each variability (Quenching, pre-stimulus or post stimulus) measure. Asterisks indicate significant correlations as assessed by a randomization analysis ($p < 0.05$, uncorrected). CB: checkerboard, CRT: choice reaction time, GNG: go-no-go, 2B: 2-back.

Signal strength and trial by trial variability

Previous studies have demonstrated that trial-by-trial variability is associated with the mean strength of the neural response (Churchland et al., 2010). To demonstrate that the findings described above are independent of between-subject differences in the mean EEG response amplitudes, we also performed the analysis using the coefficient of variation (CV: trial-by-trial variability divided by the mean EEG response, see Materials and Methods). As with trial-by-trial variability (Figure 2), the CV also exhibited a strong reduction following stimulus presentation, within the same time-window, across all four experiments (Figure 7).

Most importantly, computing the CV in equivalent pre (-200 to 0ms) and post (150 to 400ms) stimulus periods for each of the subjects revealed significant correlations across sessions (Quenching: $0.61 < r(24) < 0.82$, pre-stimulus: $0.48 < r(24) < 0.77$, post stimulus: $0.61 < r(24) < 0.76;\ p < 0.02$) and across all task pairs (Quenching: $0.59 < r(24) < 0.91$, pre-stimulus: $0.41 < r(24) < 0.65$, post stimulus: $0.5 < r(24) < 0.78;\ p < 0.05$) except for the following: Checkerboard and CRT (Quenching: $r(24) = 0.37, p = 0.07$; pre-stimulus: $r(24) = 0.26, p = 0.23$; post-stimulus: $r(24) = 0.25, p = 0.24$), Checkerboard and Go-no-go (post-stimulus: $r(24) = 0.28, p = 0.18$), and Checkerboard and 2-back (pre stimulus: $r(24) = 0.37, p = 0.08$; post-stimulus: $r(24) = 0.36, p = 0.08$). Note that even in these exceptions, correlations were always positive and most were close to significant.

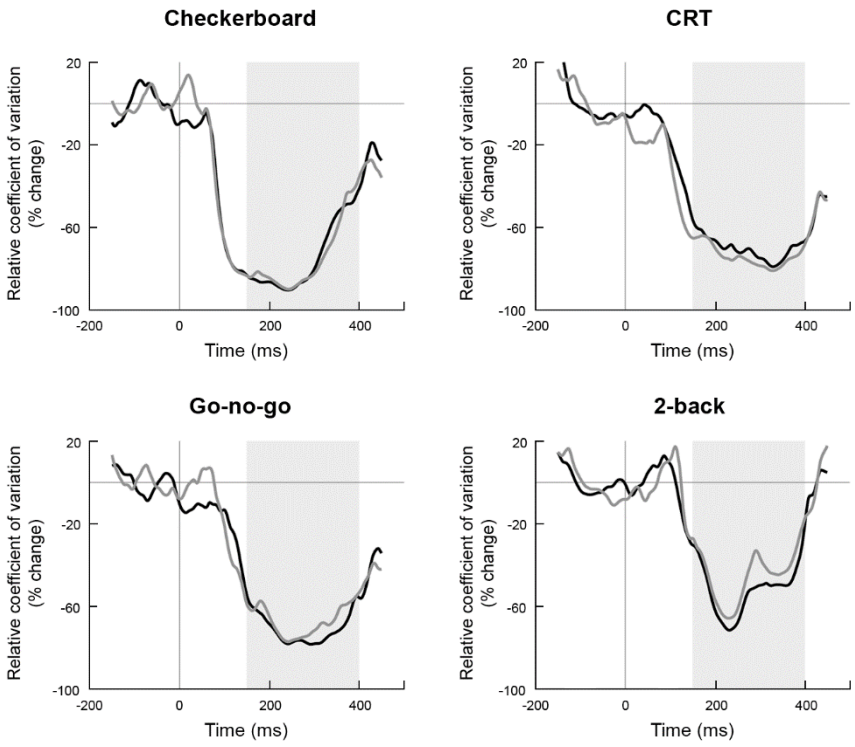

Figure 7: Temporal dynamics of the coefficient of variation (CV) in percent change units relative to pre-stimulus period. Each panel presents results from a single experiment in the first (black) and second (gray) experimental sessions. Gray background: time window (150-400ms) of sustained variability quenching that was selected for the previous analyses (Figures 2-5).

Alternative sources of trial-by-trial variability

We examined whether non-neural sources of variability, such as gaze variability or the quality of EEG recordings could explain our results regarding consistency across tasks or sessions. We utilized eye tracking data from the checkerboard experiment to demonstrate that individual magnitudes of neural variability quenching were not significantly correlated with gaze position variability in either the first ($r(21) = -0.14, p = 0.26$) or second ($r(21) = -0.28, p = 0.1$) recording session. Furthermore, re-running our analysis after regressing out individual measures of gaze position variability revealed equivalent results to those described above (Figure 3&4). Specifically, variability magnitudes remained correlated over time (Quenching: $r(21) = 0.78, p = 0.3x10^{-4}$; Pre stimulus: $r(21) = 0.76,\ p = 0.6x10^{-4}$; Post stimulus: $r(21) = 0.6, p = .0036$). This reassured us that the consistent magnitudes of neural variability described above were not associated with the ability of the subjects to maintain fixation.

To demonstrate that our results were not due to individual differences in the quality of the EEG recordings, we computed the electrode offset variability (see Materials and Methods). Electrode offset variability, was not significantly correlated with the

magnitude of variability quenching in any of the experiments performed in either the first or second session ($-0.26 < r(24) < 0.21, p > 0.11$). Furthermore, re-running our analysis after regressing out individual magnitudes of electrode offset variability revealed equivalent results to those described above (Figure 3&4). Specifically, variability magnitudes remained correlated over time (Quenching: $0.8 < r(24) < 0.89$, Pre stimulus: $0.76 < r(24) < 0.92$, Post stimulus: $0.59 < r(24) < 0.92$; $p < 0.003$) and across tasks (Quenching: $0.57 < r(24) < 0.93$, Pre stimulus: $0.73 < r(24) < 0.76$, Post stimulus: $0.76 < r(24) < 0.94, p < 0.004$).

Discussion

Our results demonstrate that neural variability magnitudes differ across adult subjects in a consistent and reproducible manner over long periods of time and across tasks with dramatically different attentional and cognitive demands. This was true for neural variability magnitudes in either pre-stimulus or post-stimulus periods and for variability quenching magnitudes (Figures 3&4, Table 1). These consistent individual differences in the magnitude of neural variability were much larger than differences across the tasks (Figure 5) despite the use of tasks with different structures, stimuli, and considerably different attentional and cognitive demands (Figure 1). Furthermore, when examining the task with the highest cognitive demands in our study, a two-back working memory task, we found that individuals with larger pre-stimulus variability, post-stimulus variability, and larger variability quenching exhibited more accurate detection of letter repeats. Taken together, these results reveal that neural variability magnitudes are mostly static individual

traits that can be modified only slightly by mechanisms of attention or neuromodulation, yet can explain differences in behavioral capabilities across subjects when the task is demanding.

Neural variability: state or trait?

To what degree is neural variability under flexible behavioral control? Previous studies have reported that actively allocating attention to a visual stimulus reduces the trial-by-trial response variability of single neurons (Mitchell et al., 2007) and the shared/correlated variability across the local neural population (Cohen and Maunsell, 2009; Mitchell et al., 2009). Indeed, it has been proposed that attention improves behavioral performance primarily by reducing correlated trial-by-trial variability/noise (Cohen and Maunsell, 2009). Additional studies have reported that raising the levels of dopamine and/or norepinephrine increases the magnitude of neural variability in both humans (Garrett et al., 2015) and animals (Aston-Jones and Cohen, 2005; Sakata et al., 2008). It has been suggested that these neuromodulatory mechanisms are associated with activation of exploration versus exploitation states. In the exploration state, the animal behaves in a more variable manner that enables learning through trial-and-error, whereas in the exploitation state the animal behaves in a more reproducible manner in order to exploit previously learned information.

While attention and neuromodulation are invaluable mechanisms for flexibly changing the magnitude of trial-by-trial neural and behavioral variability, individual differences in neural variability magnitudes are also governed by many other neurophysiological mechanisms. At the single cell level, these include the noisy

response characteristics of peripheral sensors (Schneeweis and Schnapf, 1999), the stochastic nature of synaptic transmission (Ribrault et al., 2011), and the dynamic changes caused by neural adaptation (Clifford et al., 2007) and synaptic plasticity (Feldman, 2009). At the neural network level, additional variability is generated by adjustments of the excitation/inhibition balance (Turrigiano, 2011) and continuous interaction and competition across large neural populations (Kelly et al., 2008). These mechanisms are likely to be the product of multiple genetic and environmental factors that create and modify developing neural circuits and eventually solidify their structure and function during specific critical periods in development (Hensch, 2005).

Our results reveal that there are large differences in neural variability magnitudes across adult subjects and clearly show that individual neural variability magnitudes are remarkably consistent across tasks and over time. This suggests that they mostly represent individual traits rather than flexible states. We speculate that examining these measures in young children would be particularly interesting for understanding how neural variability may change during development and then stabilize in adolescence or adulthood. Analogous behavioral research in humans (MacDonald et al., 2006) and birds (Ölveczky et al., 2011) has already shown that behavioral variability diminishes during early development and stabilizes in adulthood.

The behavioral significance of neural variability

There is ongoing debate regarding the potential behavioral significance of different measures of neural variability. On the one hand, several studies have demonstrated that smaller trial-by-trial neural variability is associated with better perceptual and

cognitive performance. For example, fMRI studies have reported that trial-by-trial variability is smaller on trials where a threshold-level stimulus is detected (Schurger et al., 2010) and on trials where a stimulus is later remembered (Xue et al., 2010) . Similarly, MEG and EEG studies have reported that neural variability quenching is larger on trials where a threshold-level stimulus is detected (Schurger et al., 2015) and in individuals with lower (better) contrast discrimination thresholds (Arazi et al., 2017) . Furthermore, excessive neural variability has been reported in different disorders including autism (Milne, 2011; Dinstein et al., 2012), ADHD (Gonen-Yaacovi et al., 2016), and schizophrenia (Yang et al., 2014), while electrophysiology studies have reported that neural responses are more variable in elderly animals (Turner et al., 2005; Yang et al., 2009) and humans (Anderson et al., 2012) who exhibit cognitive decline. These results are in line with signal detection theory principles, which suggest that intrinsic variability/noise reduces the detection and discrimination abilities of a perceptual system (Green and Swets, 1966).

Other studies, however, have reported that younger individuals exhibit larger fMRI time-course variability than elderly individuals (Garrett et al., 2010) and that this coincides with faster and more consistent responses when performing cognitive tasks such as perceptual matching, attentional cueing, and delayed match to sample (Garrett et al., 2013). It has been proposed that such increased ongoing variability may be beneficial for cognitive performance, because it allows for higher neural complexity and enables a neural network to flexibly switch between different states (McIntosh et al., 2008). A possible compromise between these potentially contradictory studies is that large ongoing neural variability together with large quenching may yield the best perceptual and cognitive performance(Schurger et al.,

2015; Arazi et al., 2017). An important conclusion from both lines of research is that it is essential to carefully de-compose neural variability into distinct components such as ongoing variability and stimulus-evoked variability when examining relationships with behavioral measures (Dinstein et al., 2015).

Our results also represent a potential compromise between the two views described above. We found significant positive correlations between the accuracy of performance on the two-back task and pre-stimulus neural variability magnitudes as well as a significant negative correlation with variability quenching magnitudes (Figure 6). This suggests that a combination of larger ongoing neural variability along with stronger variability quenching are associated with better behavioral performance. These effects were only found with respect to the two-back task, which was the hardest task in our study (Figure 1). We speculate that this evidence suggests that individual differences in neural variability magnitudes exhibit a behavioral impact mostly in tasks that involve considerable attentional and cognitive loads.

Signal strength and trial-by-trial variability

Previous electrophysiology studies have demonstrated that trial-by-trial variability scales with the mean amplitude of the examined neural responses (Shadlen and Newsome, 1994). To examine trial-by-trial variability independently of the mean response most electrophysiology studies, therefore, use the Fano Factor or the coefficient of variation (CV), which normalize trial-by-trial variability by the mean response (Churchland et al., 2010; Goris et al., 2014). Animal studies, however, have rarely examined the behavioral impact of neural variability magnitudes.

In contrast, human neuroimaging studies that have examined the relationship between response variability and behavior using fMRI and EEG have rarely reported CV (Garrett et al., 2013, 2015; He and Zempel, 2013; Gonen-Yaacovi et al., 2016; Arazi et al., 2017). Nevertheless, to relate our findings to both literatures, we carried out our analyses once using trial-by-trial variability measures and again using the CV measure. We found almost equivalent results in both cases, which revealed that large between-subject differences in variability magnitudes are consistent across experimental sessions and tasks even when normalizing trial-by-trial variability by the mean EEG response. Consistent differences in neural variability magnitudes across subjects are, therefore, likely to reflect differences in underlying physiological mechanisms that are specific to the variability of neural activity rather than the strength of neural activity.

Measurement noise

Measures of trial-by-trial neural variability may be biased by subject-specific measurement noise of non-neural origin. We examined two potential sources of non-neural variability in our study: eye-gaze variability (indicative of the stability of fixation across trials) and trial-by-trial variability in electrode offset (indicative of the stability of the EEG recording). We did not find any significant correlation between electrode-offset variability or gaze-position variability and neuronal measures of variability. Furthermore, regressing out individual magnitudes of electrode offset variability or gaze position variability did not alter the results. These additional analyses demonstrate that the individual magnitudes of trial-by-trial variability were not associated with these potential sources non-neural measurement noise. With

that said, additional studies examining the consistency of individual neural variability magnitudes across different neuroimaging techniques (e.g., fMRI and EEG) would be necessary for demonstrating the potential robustness of these findings across techniques with different types/sources of measurement noise.

Conclusions and future directions

This study adds to accumulating evidence demonstrating that neural variability measures of individual subjects are remarkably useful for understanding their individual behavioral capabilities. While neural variability is to some degree under flexible control of attention and neuromodulation, our results demonstrate that neural variability magnitudes are mostly consistent across distinct tasks and recording sessions. We, therefore, propose that neural variability magnitudes represent stable between-subject differences in fundamental neural characteristics that were likely forged by genetics and environmental exposures during early development. Revealing how neural variability magnitudes develop during childhood and how they may be manipulated in adulthood are likely to be of great interest for further basic and clinical research (Dinstein et al., 2015).

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