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Neural variability quenching during decision-making: Neural individuality and its prestimulus complexity

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A B S T R A C T

The spontaneous activity of the brain interacts with stimulus-induced activity which is manifested in event-related amplitude and its trial-to-trial variability (TTV). TTV describes the variability in the amplitude of the stimulus-evoked response across trials, and it is generally observed to be reduced, or quenched. While such TTV quenching has been observed on both the cellular and regional levels, its exact behavioral relevance and neuronal basis remains unclear. Applying a novel paradigm for testing neural markers of individuality in internally-guided decision-making, we here investigated whether TTV (i) represents an individually specific response by comparing individualized vs shared stimuli; and (ii) is mediated by the complexity of prestimulus activity as measured by the Lempel-Ziv Complexity index (LZC). We observed that TTV - and other electrophysiological markers such as ERP, ERSP, and ITC – showed first significant differences between individualized and shared stimuli (while controlling for task-related effects) specifically in the alpha and beta frequency bands, and secondly that TTV in the beta band correlated significantly with reaction time and eLORETA activity. Moreover, we demonstrate that the complexity (LZC) of neuronal activity is higher in the prestimulus period while it decreases during the poststimulus period, with the former also correlating specifically with poststimulus individualized TTV in alpha (but not with shared TTV). Together, our results show that the TTV represents a marker of 'neural individualization' which, being related to internal processes on both neural and psychological levels, is mediated by the information complexity of prestimulus activity. More generally, our results inform the pre-post-stimulus dynamics of rest-stimulus interaction, which is a basic and ubiquitous neural phenomenon in the brain and highly relevant for mental features including their individuality.

1. Introduction

1.1. General background – variability as marker of neural and psychological individuality

Variability in brain activity between participants has long been treated as meaningless noise or measurement error (Arazi et al., 2017a; Seghier and Price, 2018). This neural variability, especially in task-evoked responses, however, has recently been shown to explain the behavioral and perceptual differences of individual participants (Haigh et al., 2015; Arazi et al., 2017b, 2017a), thus challenging this view. The finding may provide measures of specifically individual features of brain activity (Arazi et al., 2017b, 2017a), and so address an urgent desire for individualized neural markers, a growing concern in both basic and clinical neuroscience (Braver et al., 2010; Reineberg et al., 2015; Friedman and Miyake, 2016; Jang et al., 2017; Seghier and Price, 2018).

What purpose, though, does a better understanding of these interindividual differences serve? Cognitive studies often show major intra- and interindividual differences in both neuronal and behavioral responses to stimuli. Given that the stimuli or tasks are the same for all subjects, one would rather expect similar changes in neural and behavioral responses across subjects, however this is not the case. It raises the question as to the origin of this interindividual variability and its neural markers. Determining these sources of variability is even more pressing in clinical settings. Here, intersubject variability may provide explanations as to why symptoms differ between patients with similar lesions, or those with the same symptoms have different outcomes (Seghier and Price, 2018). Investigating these differences may shed light on the underlying mechanisms of these clinically significant variances.

Variability of task-evoked activity, as manifested in trial-to-trial variability quenching, has been consistently observed on multiple levels of neural activity, including cellular recordings (Arieli et al., 1996;

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Monier et al., 2003; Finn et al., 2007; Churchland et al., 2010, 2011; Hussar and Pasternak, 2010; Scaglione et al., 2011; Chang et al., 2012; White et al., 2012; Goris et al., 2014; Mazzucato et al., 2015, 2016; Liu et al., 2016), electroencephalography/electrocorticography (EEG/ECoG) (He and Zempel, 2013; Schurger et al., 2015; Arazi et al., 2017b, 2017a), and functional magnetic resonance imaging (He, 2013; Ferri et al., 2015; Huang et al., 2017a) (see also (Dinstein et al., 2015) for review of TTV). These data demonstrate that TTV quenching is a ubiquitous phenomenon of neural activity and is a result of a nonlinear interaction between the brain's ongoing spontaneous activity and activity induced by the stimulus (He, 2013; Huang et al., 2017a). The exact behavioral relevance and underlying neuronal mechanisms of TTV quenching, however, remain unclear.

In humans, this quenching of activity is unchanging in the individual over time and across tasks (Arazi et al., 2017b), and is related to behavioral performance (He and Zempel, 2013; Haigh et al., 2015; Schurger et al., 2015; Arazi et al., 2017a, 2017b); stronger TTV quenching is associated with faster reaction times (He, 2013), superior perceptual abilities (Schurger et al., 2015; Arazi et al., 2017b; Baria et al., 2017), and superior memory recall (Xue et al., 2010). When taken together, these results suggest that TTV quenching is strongly related to internal - individual or self-specific - neural processing; TTV may thus be a marker of an individualized neural response.

What, however, are the sources of TTV? It has been shown that prestimulus (He, 2013) and resting state activity (Huang et al., 2017a) influence trial-to-trial variability, which suggests that TTV is partly due to internal - pre-stimulus - rather than external - stimulus-related - sources. The influence of the two – internal and external – implies that TTV is a hybrid of the impact of both internal prestimulus activity levels and external stimulus-related effects (Huang et al., 2017a). To test this hypothesis, we require an operational distinction between the effects of internal activity and those of the external stimulus on the commonly shared output, the stimulus-induced or task-evoked activity in the post-stimulus period.

The operational distinction between internal and external effects can, on a psychological level, be studied comparing internally-guided (IDM) and externally-guided decision-making (EDM) (Nakao et al., 2009, 2012, 2013a). In IDM, no correct answer based on external criteria exist; participants respond based on their own internal preferences – this reflects individuality on a psychological level (Nakao et al., 2012). In contrast, in EDM there is one correct answer based on external criteria (Nakao et al., 2012) as would be the case if given two words and asked which was longer (Nakao et al., 2009). These studies show differential neural correlates for IDM and EDM (Nakao et al., 2012, 2013a, b, 2016); the differential impact of IDM and EDM on TTV, as well as potentially different roles of pre-stimulus activity, however, remain to be studied. We therefore combine here an investigation of TTV and pre-stimulus effects in the context of IDM vs EDM to probe for the neural correlates of internal and external effects on TTV.

1.2. Main aim – internal prestimulus origin of poststimulus trial-to trial variability

The main aim of our study, then, was to determine if internal, pre-stimulus ongoing neural activity contributes to the source of task-evoked variability as measured with TTV. We hypothesize that TTV is a marker of neural individuality as it can originate only from the internal neural activity and, more specifically, its pre-stimulus complexity (see below). To test this hypothesis, we converged an IDM/EDM paradigm with TTV measures and analysis of pre-stimulus activity; this allowed us to study the internal and external sources of individuality with respect to TTV on both the neural and psychological levels.

A study in which participants were presented with identical stimuli - in one condition they made internally guided decisions while the second condition demanded externally guided decisions (Nakao et al., 2009, 2012, 2013a) – was designed to specifically investigate this question. The IDM condition employed here was a task adapted from previous studies (Sarlo et al., 2012; Manfrinati et al., 2013; Pletti et al., 2016) and cited as an example of IDM which allowed us to test for individuality on the psychological level of the task (Greene, 2001; Greene et al., 2004; Moll et al., 2006, 2008; Moll and de Oliveira-Souza, 2007; Greene and Paxton, 2009; Nakao et al., 2012).

To further test the specificity of TTV quenching, participants were presented with four stimuli, two individualized to them and two shared by all participants (Wolff et al., 2018), similar to the high- and low-conflict stimuli used in a past IDM/EDM study (Nakao et al., 2013a). In this 2×2 factorial design, our aim was to determine if TTV quenching was significantly different in IDM when compared to EDM, and if there was a difference – across conditions or specific to one condition – in TTV between individualized stimuli and stimuli shared by all participants. This allowed us to operationalize individuality on the psychological level with respect to both task – IDM vs EDM – and stimuli – individualized vs shared.

TTV quenching is related to event-related desynchronization which has been shown in alpha, beta and gamma (Arazi et al., 2017a). Specifically, the alpha frequency band seems to exhibit a special role for individuality as it has long been shown to be highly individual (Posthuma et al., 2001; Klimesch et al., 2007; Bröltzner et al., 2014; Gruber et al., 2014; Mierau et al., 2017) and related to self-related stimuli (Bai et al., 2016). For that reason, we investigated TTV quenching in specific frequency bands, with a specific focus on alpha as a possible marker of neural individuality. That extends previous TTV investigations that have been conducted only in the broadband, not in specific frequency bands such as alpha.

1.3. Specific aims – TTV as individual neural marker and its pre-stimulus complexity

The first specific aim of our EEG study consisted in testing TTV as an individual neural marker by applying a novel study design in an IDM paradigm (Lieberman and Pfeifer, 2005; Volz et al., 2006; Nakao et al., 2012, 2016). We hypothesized that there would be significant differences in TTV quenching - specifically in alpha, beta and gamma bands previously shown to correlate with decreases in power (Arazi et al., 2017b) - as well as differences in other electrophysiological markers (ERP, ERSP, ITC) in response to individualized stimuli compared to stimuli shared by all participants.

In addition to its modulation by different stimuli (Churchland et al., 2010, 2011; Hussar and Pasternak, 2010; Arazi et al., 2017b), TTV is also dependent upon the degree of the brain's internal prestimulus variance as observed on both cellular (Kisley and Gerstein, 1999; Curto et al., 2009; Schurger et al., 2010; Pachitariu et al., 2015) and regional levels (He, 2013; Schurger et al., 2015; Huang et al., 2018). This strongly suggests that features of the prestimulus activity, such as its complexity, mediate TTV quenching.

Based on these findings, the second aim of our study was to characterize prestimulus activity in terms of its informational complexity. This was achieved by applying the well-known Lempel-Ziv complexity measure (LZC) (Lempel and Ziv, 1976) which has been used widely in EEG/MEG studies (Fernández et al., 2009, 2011; 2012; Takahashi, 2013; Ibáñez-Molina et al., 2015; Mateos et al., 2018). We hypothesized that the degree of prestimulus complexity, as measured through LZC (Mateos et al., 2018), is directly related to the degree of TTV quenching in response to individualized (rather than shared) stimuli.

Notably, to disentangle internal (prestimulus) and external (stimulus-related) effects on TTV, we introduced a novel method for TTV calculation in EEG by calculating TTV independent of the variance at stimulus onset. This would confound prestimulus effects and TTV calculation. This was accomplished by using pseudotrials - trials when a stimulus is absent (Huang et al., 2017a,b) - to compare with actual trials and to calculate poststimulus variability through TTV (see Huang et al., 2017a,b for an analogous method in fMRI).

1.4. Overview – from ERP, ERSP, and ITC over TTV to pre-stimulus Lempel-Ziv complexity

We recorded electroencephalography (EEG) and response activity in human subjects while they performed a visual IDM and EDM task adapted from previous studies (Sarlo et al., 2012; Manfrinati et al., 2013; Pletti et al., 2016). To individualize two of the four stimuli presented in the EEG session, a behavioral session was completed prior to it to determine the response thresholds of the participants. As done in a previous study (Arazi et al., 2017a), we started by measuring event-related potentials (ERPs) to determine that there was an effect of the stimuli on evoked activity. Next, we measured the event-related spectral perturbation (ERSP) and intertrial coherence (ITC) to establish if there were differences between stimuli or conditions in frequency band power and phase consistency, and if so, which bands.

We then measured TTV by calculating the TTV index, a new measure, which incorporates pseudotrials (Huang et al., 2017a), and investigated the effect of stimulus and condition in the broadband and individual frequency bands. In only those bands found to have significant differences, we correlated the TTV index values to the response-related measures from the EEG session (threshold, reaction time) to see if our neural measure related to the behavior of the individual participants. Finally, we measured LZC in the internal prestimulus activity and correlated it with the TTV index values in the significant bands; this served the purpose of determining if, and for which stimulus or condition, the prestimulus complexity relates to the poststimulus effect of the external stimulus.

2. Methods

2.1. Participants

Thirty-four right-handed (Oldfield, 1971) participants (age: mean = 30.6 ± 11.0 years, range = 18–55 years; 18 female) completed this study. All participants were free of psychiatric diagnoses or history of psychiatric illness, neurological illness or history of head injury, and had perfect or corrected-to-perfect vision. The experimental protocols were approved by the research ethics committee of the University of Ottawa Institute of Mental Health Research (REB # 2009018), and the study was carried out with their permission. Written informed consent was obtained from each participant prior to study participation.

2.2. Determining individualized stimuli

For the EEG session, two of the four stimuli presented were individualized according to a response threshold in the IDM condition. The IDM task was a consequential moral dilemma adapted from previous studies (Sarlo et al., 2012; Manfrinati et al., 2013; Pletti et al., 2016) as an example of IDM (Greene, 2001; Greene et al., 2004; Moll et al., 2006, 2008; Moll and de Oliveira-Souza, 2007; Greene and Paxton, 2009; Nakao et al., 2012).

The moral dilemma scenarios presented a situation in which participants would push some strangers to their deaths to save another group of strangers. They were adjusted from EEG studies (Sarlo et al., 2012; Manfrinati et al., 2013; Pletti et al., 2016) only to generalize the number of bystanders and victims. The purpose of this was to determine the maximum acceptable ratio of people killed to people saved in the scenario for each participant. Since we were varying the number of bystanders sacrificed and the number of victims saved, the text was changed from specific numbers to ‘several’, ‘some’, and so on.

After the participants had read the scenario at their own pace, the stimuli presented were composed of twelve two-dimensional stick-people on the left and right side of the screen, with a white line and a fixation cross down the middle separating both (Fig. 1A). The number of people on the left side represent the number of people that are killed in the scenario, and the number on the right side denote the number of people that are saved because of the others dying.

The task of the participant in this threshold determining behavioral block – as well as during the IDM task of the EEG session - was to decide whether the ratio presented was acceptable to them. Each stimulus was presented for 2 s and their response took the form of either a YES or NO, with the left and right arrow key being counterbalanced across participants as to which constituted a YES response. The participants were presented with 10 repetitions of each stimulus, in a random order. All stimuli included twelve two-dimensional people however the ratio between the left and right side differed. A fixation cross was presented between each stimulus as the intertrial interval with a jittered duration of 5000 ms, 5500 ms or 6000 ms.

To calculate the response threshold of each participant, two sigmoid functions were fit, one to the YES responses and one to the NO responses using the *glmfit* function in MATLAB (Fig. 1B). The point at which these two functions cross was determined to be their threshold. Therefore, the stimulus immediately below and above the threshold were the individualized stimuli presented in the EEG session while two stimuli at the extreme ends of the ratios (1:11 and 10:2, all participants responded YES and NO consistently during the behavioral session) were presented to all participants as the shared stimuli (Fig. 1C). For all 34 participants, there was variability in the response threshold with each participant falling under one of five thresholds (Fig. 1D).

2.3. EEG session

EEG recordings were made using a 64-channel Quik-Cap (Compumedics, Charlotte, NC, USA). Additional channels were added for offline referencing (mastoids) and Independent Component Analysis (ICA) decomposition (vertical and horizontal ocular). The impedance of all channels was measured at less than 5kΩ before recording was initiated. During analysis, all files were re-referenced to the average of the two (left, right) mastoids.

Participants were seated in a dark, quiet room, between 55 and 60 cm away from the computer screen, as per their comfort. The experimental paradigm was presented using E-Prime 2.0 software (Psychology Software Tools, Inc., Sharpsburg, PA, USA). The EEG data was recorded with no high-pass, low-pass or notch filters at a sampling rate of 1 kHz and referenced online to the right mastoid.

The EEG session was identical to the behavioral session, with two important differences: 1) the participant was only presented with four stimuli (two shared by all participants and two individualized (Fig. 1C)), and 2) each scenario had two blocks of 60 trials, with each stimulus repeated 15 times per block. All participants were presented with two stimuli to which they had responded YES more than 80% of the time – 1:11 and just below threshold – and two stimuli to which they had responded NO more than 80% of the time – above the threshold and 10:2. The order of scenarios was counter-balanced across participants.

For EDM blocks, the same stimuli were presented, though the task was different as is consistent with previous IDM/EDM paradigms (Nakao et al., 2009, 2013b). The participant was asked whether there were more people on the left side of the screen than the right side. The same number of trials, same ITI, and same scenarios were presented before the beginning of the trials. The order of the IDM or EDM blocks was counter-balanced across participants.

2.4. EEG preprocessing

All EEG data preprocessing was completed using EEGLAB (v12, v13) (Delorme and Makeig, 2004), which required MATLAB (The MathWorks) v2018a, including the use of the Optimization, Statistics and Signal Processing Toolboxes. All statistical analysis (except for the event-related spectral perturbation and intertrial coherence measures) was completed using SPSS v24 (IBM).

Data was resampled to 500 Hz using EEGLAB's *resample* function. The continuous data was then low- and high-pass filtered (FIR filter) from 0.5 Hz to 70 Hz, and a notch filter applied at 60 Hz to eliminate electrical

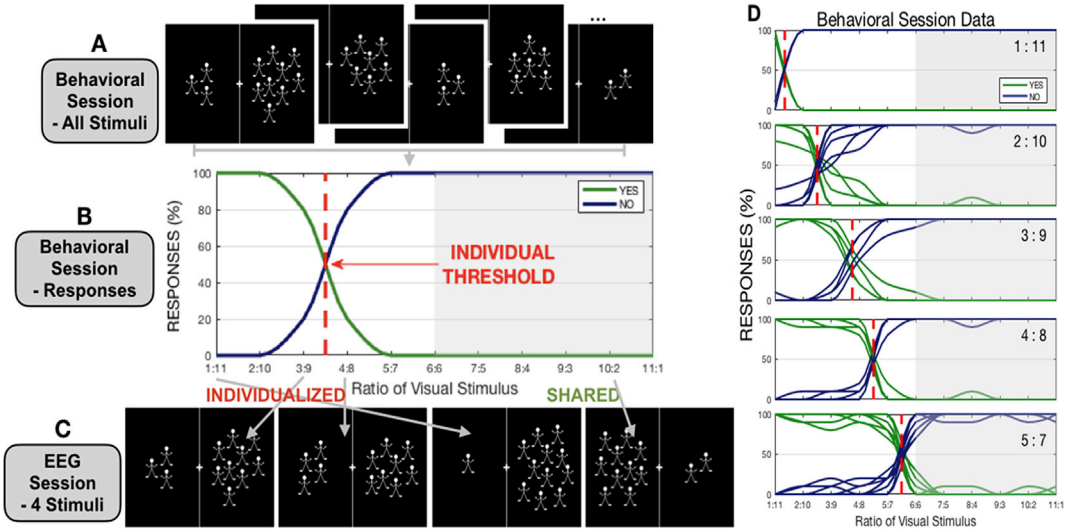

Fig. 1. Study threshold determination and behavioral session results. **A)** Determination of threshold in behavioral session. Participants read a scenario (see Wolff et al., 2018) in the behavioral session. Participants were presented with 10 repetitions of each stimulus. **B)** Based on the percentage of YES and NO responses for each stimulus in the behavioral session, the threshold (dashed red vertical line) was calculated. **C)** The stimuli immediately below and above the threshold - the individualized stimuli - as well as two other stimuli shared by all participants - 1:11 and 10:2 - were the only stimuli presented to participants in the subsequent EEG session. **D)** Response results from the behavioral session for all participants. Thresholds were calculated in MATLAB using their *glmfit* function. Five participants had a threshold of 1:11, 2:10, and 4:8, while four participants had one of 3:9. The largest group was 5:7 with fifteen participants.

line noise.

The data was then visually inspected. If channels were flat longer than 5s, had less than 0.80 correlation with neighboring channels, or had line noise greater than 4 standard deviations difference compared to other channels, they were removed. The mode of channels removed for all participants were 2, with the range being 0 to 5.

The continuous data was then epoched with a baseline of −200 ms to stimulus onset. All files were referenced to the average of the two mastoids. All stationary artifacts, specifically eye movements, were reduced using Independent Component Analysis (ICA) and the Multiple Artifact Rejection Algorithm (Winkler et al., 2011, 2014).

2.5. Event-related potential, event-related spectral perturbation and intertrial coherence analysis

To begin, we measured two event-related potential (ERP) components to establish the effect of stimulus and condition: the N100 and the P300. Both components were measured at electrode Pz which was determined according to previous literature (Chen et al., 2009; Veit et al., 2013; Wang et al., 2014; Cui et al., 2016; Gan et al., 2016) and visual inspection of the ERP grand average waveforms for both conditions and groups of stimuli. The peak amplitude of each component was measured in a 2×2 (condition, stimulus) repeated measures ANOVA from time intervals taken from previous studies (Chen et al., 2009; Veit et al., 2013): 100–220 ms for the N100, 350–450 ms for the P300.

After finding a significant effect of stimulus in the ERP analysis, event-related spectral perturbation (ERSP) and intertrial coherence (ITC) was measured from stimulus onset to 450 ms (end of P300 interval) at the same electrode. This was done to determine if there was a difference in frequency band power and phase coherence between conditions or stimuli, and if so, in which bands.

A three-cycle Morlet Wavelet analysis was employed in EEGLAB, with a Hanning tapered window. For these two measures, statistical differences were calculated in EEGLAB with a paired sample *t*-test using its statistics (significance level of 0.05) and applying the False Discovery Rate (Benjamini and Hochberg, 1995) to account for multiple comparisons.

To determine if there was a difference in activity related to the response, an ERP and ERSP at Pz was time-locked to the response in each trial. A repeated measures *t*-test found no significant difference between the conditions or stimuli.

For ITC, the coherence for each stimulus in each condition was extracted between 0 and 100 ms and between 3.92 and 6.13 Hz (the nearest data points between 4 and 6 Hz) to measure correlations with ERP peak amplitudes (Fig. 3B and C). The data was extracted from 0 to 100 ms due to the significant results found in the ITC analysis in Fig. 3B.

2.6. Trial-to-trial variability index calculation

Next, we measured trial-to-trial variability (TTV) to investigate the quenching of neural activity after stimulus onset. In this study, TTV was measured as the variability changes with respect to stimulus onset (see (He and Zempel, 2013; Arazi et al., 2017a, 2017b) for related methods). This method allowed for the calculation of a time-resolved TTV; each poststimulus timepoint measured variability relative to stimulus onset. In addition, to separate effects in the TTV related to the stimulus from the effects of ongoing variability, the use of pseudotrials (Huang et al., 2017a), trials without a stimulus (Dinstein et al., 2015), were used.

Pseudotrials were calculated from the intertrial intervals (ITIs) in which a virtual stimulus was inserted (Fig. 4A). ITIs were jittered to be 5s, 5.5s and 6s while the stimulus duration was 2s, so pseudotrials were inserted during this ITI period. The actual trials – and therefore the pseudotrials – were extracted from 500 ms prior to stimulus onset until 2s after stimulus onset. For a 5s ITI, the pseudo stimulus onset was inserted 3.5s prior to the actual stimulus onset. Before this, a 1s buffer between the actual trial and the pseudo trial was taken to allow for any activity related to the fixation cross onset to return to baseline. In the 5.5s and 6s ITIs, the buffer between the pseudotrial and the actual trial increased from 1s in the shortest ITI to 1.5s and 2s in the longest.

Though neural activity was only analyzed from stimulus onset to 450 ms, the duration of the stimulus continued to 2000 ms. From the inserted pseudotrials, TTV of the pseudo stimulus was calculated in the same way as the actual stimulus (Fig. 4A) (see Huang et al., 2017a,b for a similar method in fMRI).

To account for the change in variability related to the stimulus itself, the pseudotrial TTV was subtracted from the actual trial TTV from 200 to

800 ms post stimulus for each timepoint (Fig. 4B). This was done to account for the ongoing spontaneous fluctuations of the neural activity, therefore correcting for this in the calculation of the TTV. The mean was then calculated, yielding one value, the TTV index.

Cognitive tasks are known to have differential effects on frequency bands (Klimesch, 1999, 2011; 2012; Jokisch and Jensen, 2007; Jensen et al., 2010, 2014; Klimesch et al., 2011; Fellinger et al., 2011; Buzsáki and Silva, 2012; Buzsáki and Wang, 2012; Zumer et al., 2014; Bonnefond and Jensen, 2015). For this reason, and the significant differences found in the ERSP (Fig. 3A) and ITC (Fig. 3B), the continuous EEG data was filtered into frequency bands before being epoched according to above methods. The frequency ranges were as follows: broadband was 0.5–70 Hz; theta was 4–8 Hz; alpha was 8–13 Hz; beta was 13–30 Hz; gamma was 30–70 Hz. The TTV index was calculated in these filtered bands in the same way as the broadband (Fig. 5, Sup Mats).

To determine if there was an effect of condition or stimulus in each band, a 2×2 (condition, stimulus) repeated measures ANOVA was calculated for each band. All *p*-values were False Discovery Rate (Benjamini and Hochberg, 1995) corrected for multiple comparisons.

2.7. Effect of threshold on TTV index

After finding significant differences in the TTV index for specific frequency bands, we sought to relate these neural measures to our behavioral data. To start, we tested whether the threshold had a significant effect on the TTV index. Participants were grouped into three groups (low, middle, high) according to their threshold only in the TTV index bands found to be significant in the above analysis. This was done to ensure that roughly an equal number of participants were in each group (low = 10 participants, middle = 9 participants, high = 15 participants).

To determine if threshold had an effect - or interaction - with either factor in the significant TTV index bands, a $2 \times 2 \times 3$ (condition, stimulus, threshold) repeated measures ANOVA, with a between subjects' factor of threshold, was done on the absolute value of the TTV index.

2.8. Reaction time correlations with TTV index

Next, to determine if the mean reaction times correlated with the TTV index in either of the significant bands, we performed one-tailed, bootstrapped (1000 samples) Pearson correlations with significance at 0.05. Since our experimental design focused on the difference between the individualized and shared stimuli, we first calculated the differences between them for each measure; the TTV indices and mean reaction times shared values were subtracted from the individualized value. This was done to emphasize the difference between them.

2.9. Lempel-Ziv Complexity analysis

As one of our aims was to determine if prestimulus activity related to our poststimulus TTV index measure, we applied a measure of complexity from information theory (Gershenson and Fernandez, 2012) to the non-baseline corrected data. Lempel-Ziv Complexity (LZC) was calculated based on previous studies (Aboy et al., 2006; Casali et al., 2013) in MATLAB v2018a using a custom script. In both the pre- and poststimulus periods for which LZC was calculated, 500 ms of the signal was measured.

To calculate LZC, the EEG signal was first converted into a binary sequence. For each data point in a timeseries $x(i)$, a symbol sequence $s(i)$ is calculated:

$$s(i) = \begin{cases} 0 \; if \; x(i) < T_d \\ 1 \; if \; x(i) \geq T_d \end{cases}$$

where T_d is the threshold (Aboy et al., 2006). In the complexity equation used here, the threshold was the median. This binary sequence $s(i)$ is then scanned from left to right and the complexity measure $c(n)$ is increased by one each time a new sequence of consecutive values occurs (Aboy et al., 2006). Finally, the complexity value $C(n)$ is normalized to control for signal length as follows:

$$C(n) = \frac{c(n)}{\frac{n}{\log_2(n)}}$$

where n is the length of the $c(n)$ sequence.

We first determined if there was a difference between the pre- and poststimulus LZC in all stimuli (Fig. 7A), the difference between these two values was calculated, and the difference between stimuli in each condition was measured (Fig. 7B). Paired-sample bootstrapped (1000 samples) *t*-tests were done for each of these tests, with the False Discovery Rate (Benjamini and Hochberg, 1995) correction applied to all *p*-values.

Finally, to determine if there was a relationship between prestimulus activity, as measured by LZC, and the TTV indices from the significant bands, one-tailed bootstrapped (1000 samples) Pearson correlations were conducted (Fig. 8), with the False Discovery Rate (Benjamini and Hochberg, 1995) applied to each correlation.

2.10. eLORETA source localization

To support our findings, we investigated whether activity in the visual cortex (due to the visual paradigm) also has a relationship with the TTV index in the significant bands. To answer this, we performed source localization using eLORETA (Pascual-Marqui, 2007) on the software of the KEY Institute at the University of Zurich (Pascual-Marqui et al., 1994). We chose one region of interest (ROI), the primary and secondary visual cortices (BA 17 and 18) and calculated the mean activity in this ROI from stimulus onset to 200 ms, the beginning of the TTV index calculation. Bootstrapped (1000 samples) one-tailed Pearson correlations between this activity and the TTV indices were performed for both stimuli and conditions, with the False Discovery Rate correction (Benjamini and Hochberg, 1995) was applied to all *p*-values to correct for multiple comparisons.

After the correlations with our main ROI, we performed a second group of correlations with three control regions. This was done to determine if our findings were specific to the visual cortices. We chose the premotor cortex (BA 6) first as it has not shown to be active during IDM tasks (Han et al., 2016) and was expected to show no difference between conditions or stimuli. The other two control regions, the posterior cingulate cortex (BA 29/30, 23/31) (PCC) and inferior parietal lobules (BA 39, 40) (IPL) are part of the default mode network and have been shown to be active during IDM tasks (Han et al., 2016; Boccia et al., 2017). If we found significant correlations in these two regions then the effect would not be specific to the visual cortices, but rather consistent across regions known to show activation during IDM tasks.

The same correlations were performed and the False Discovery Rate correction (Benjamini and Hochberg, 1995) was applied to all *p*-values.

3. Results

3.1. Threshold determination

The threshold of each participant was determined in the behavioral session prior to EEG recording. It was calculated in MATLAB from two sigmoid functions fit to the YES and NO responses of each participant. The point at which the two functions crossed was determined to be the threshold (Fig. 1B, D).

Variability across participants was shown by the resulting thresholds. The distribution was the following: five participants had a threshold of one to eleven (1:11); five participants had 2:10; four participants had 3:9; five had 4:8; fifteen had a threshold of 5:7.

3.2. Event-related potentials

To determine if there were differences in the ERPs related to condition or stimulus, a 2 (condition: IDM, EDM) x 2 (stimulus: Individualized, Shared) repeated measures ANOVA on the peak amplitudes for both components was calculated (Fig. 2).

In the early component, there was a significant effect of stimulus (Wilks' Lambda = 0.639, $F(1,33) = 18.670$, $p < .000$), but not of condition (Wilks' Lambda = 0.970, $F(1,33) = 1.028$, $p = .318$)(Fig. 1A and B). The same results were found in the late component. There was a significant effect of stimulus (Wilks' Lambda = 0.790, $F(1,33) = 8.771$, $p = .006$), while no such difference was seen between conditions (Wilks' Lambda = 1.000, $F(1,33) = 0.000$, $p = .996$)(Fig. 1A, C).

In sum, peak activity from individualized stimuli was significantly greater than shared in the N100, while the opposite was found in the P300.

3.3. Event-related spectral perturbation

From the significant ERP findings, we sought to measure changes in the frequency power due to stimulus onset. To do so, the event-related spectral perturbation (ERSP) between stimuli for each condition was measured. There was a significant effect of stimulus for the following time intervals: from 140 to 263 ms between 11.5 and 14 Hz, and between 8.5 and 10.5 Hz from 415 to 500 ms in the IDM condition (Fig. 3A).

Therefore, a difference in alpha power between individualized and shared stimuli was found in the IDM condition.

3.4. Intertrial coherence

After finding significant differences in frequency power, we next wanted to examine the effect of stimuli and condition on phase. To examine phase consistency across trials, intertrial coherence (ITC) between stimuli was measured.

There was a significant difference between 3 and 6 Hz from stimulus onset to 200 ms (Fig. 3B). Next, to determine if there was a significant effect of stimulus or condition on all stimuli, the first 100 ms of ITC for each stimulus in each participant was extracted (Fig. 3C). This time range was chosen due to the significant results found in the ITC analysis in Fig. 3B. The frequency range was also from the significant ITC results, and those specific frequencies were the datapoints nearest to the whole numbers in which we found results (there was no datapoint for 4 Hz, so 3.92 Hz was the nearest datapoint).

This data was analyzed in the same way as the ERP amplitude values, using a 2 (condition: IDM, EDM) x 2 (stimulus: Individualized, Shared) repeated measures ANOVA. It was found that there was a significant effect of stimulus (Wilks' Lambda = 0.573, $F(1,33) = 24.558$, $p < .000$), but not of condition, (Wilks' Lambda = 0.990, $F(1,33) = 0.334$, $p = .567$).

Taken together, delta/theta ITC was significantly different between stimuli - individualized vs shared - but not between conditions - IDM vs EDM.

3.5. TTV index

To measure the variability across trials related to stimulus onset, a new index, the trial-to-trial variability (TTV) index, was calculated. The TTV index – TTV in the actual trials minus TTV in the pseudotrials - was calculated in broadband and each individual frequency band to measure neural variability quenching related to stimulus onset.

For each frequency band, a 2 (condition: IDM, EDM) x 2 (stimulus: Individualized, Shared) repeated measures ANOVA was calculated to determine if there was an effect of condition or stimulus. Neither the

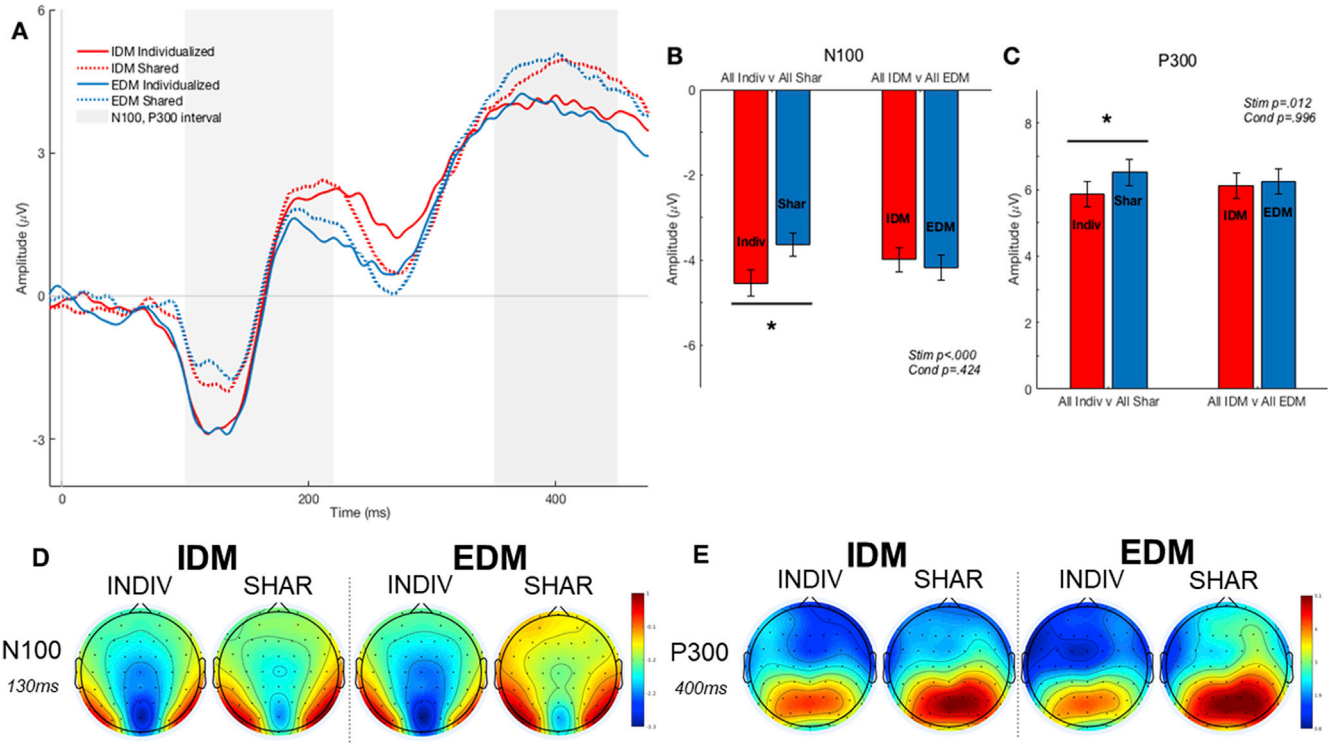

Fig. 2. Event-related potentials (ERPs) at electrode Pz. **A)** Early N100 and late P300 ERP components. **B)** The minimum amplitude between 100 ms and 220 ms (left shaded area) was measured for the N100 while the maximum amplitude between 350 ms and 450 ms (right shaded area) was measured for the P300. When all individualized stimuli were compared with all shared in the early component, a significant effect of stimulus was found ($p < .000$). When all IDM stimuli were compared with all EDM, no significant effect of condition was found ($p = .424$). **C)** The same results were found in the late component, with a significant effect of stimulus ($p = .012$), but no significant effect of condition ($p = .996$). **D)** Topographical maps for the N100 component at 130 ms. **E)** Topographical maps for the P300 component at 400 ms. *P*-values are Benjamini-Hochberg FDR corrected for multiple comparisons.

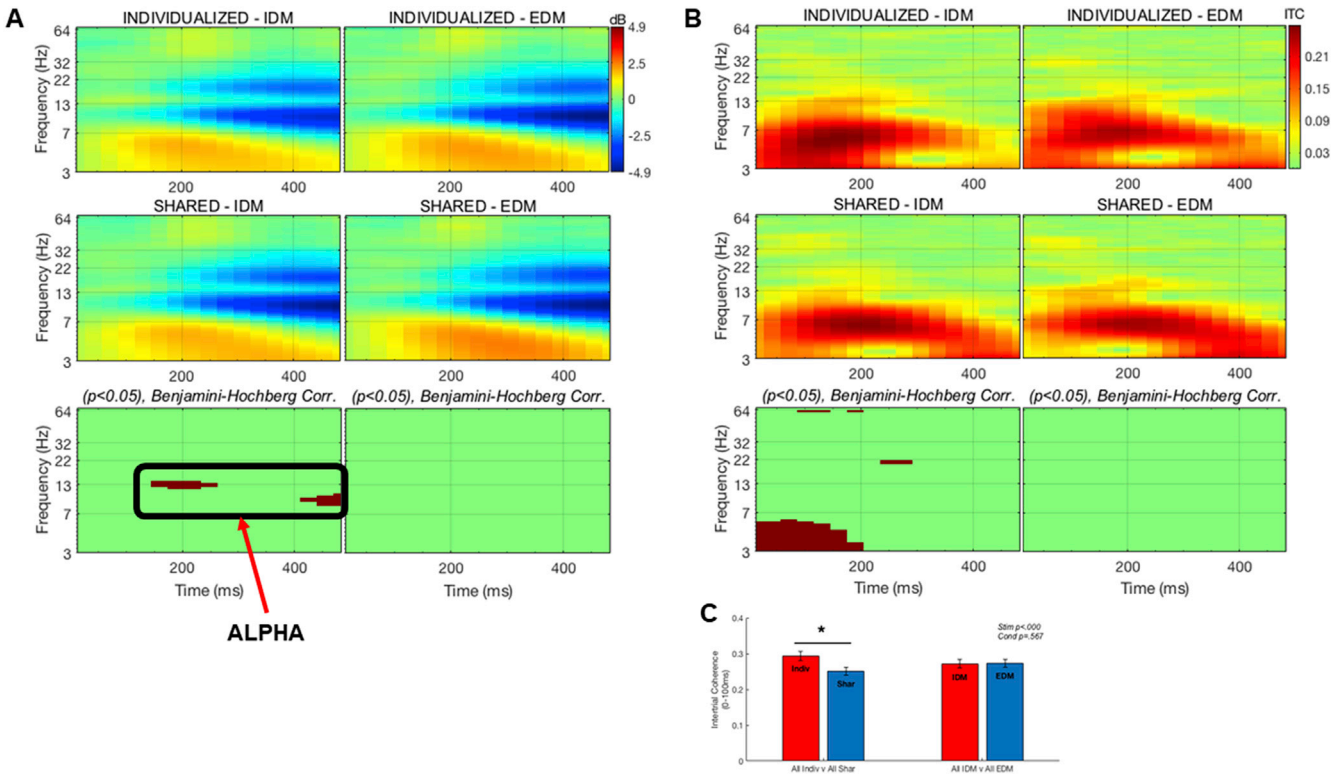

Fig. 3. Event-related spectral perturbation (ERSP) and intertrial coherence (ITC) of individualized and shared stimuli in both conditions at electrode Pz. **A)** There was a significant effect of stimulus between 140 ms to 263 ms and 415 ms–500 ms in the alpha band in the IDM condition. **B)** There was a significant difference between individualized and shared stimuli in the IDM condition between 3 and 6 Hz from stimulus onset to 200 ms. **C)** The first 100 ms of ITC for each stimulus in each participant was further analyzed for both stimulus and condition related effects. There was a significant effect of stimulus on ITC, but not of condition. *P*-values are Benjamini-Hochberg FDR corrected for multiple comparisons.

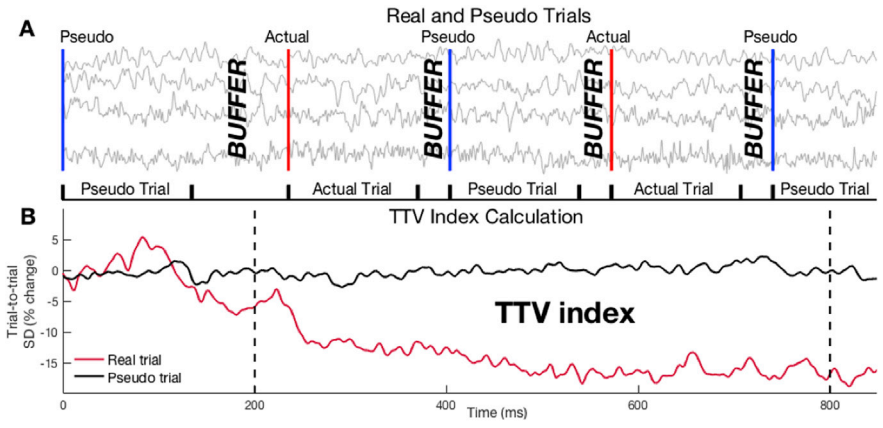

Fig. 4. Pseudotrial placement and trial-to-trial variability (TTV) index calculation. **A)** Pseudotrials are calculated from periods of the intertrial intervals (ITIs) in which a virtual stimulus was inserted. For a 5s ITI, the pseudo stimulus onset was inserted 3.5s prior to the actual stimulus onset. Before this, a 1s buffer between the actual trial and the pseudotrial was taken, with the pseudo stimulus onset (0 ms) in the 5s ITI inserted 3.5s prior to the actual stimulus. In the 5.5s and 6s ITI's, the buffer between the pseudotrial and the actual trial increased from 1s in the shortest ITI to 1.5s and 2s in the longest. From the pseudotrials, TTV of this pseudo (or surrogate) stimulus was then calculated in the same way as with the actual stimulus (see Huang et al., 2017a,b for a similar method in fMRI). **B)** To account for the change in variability specifically related to the stimulus itself, the pseudotrial TTV was subtracted from the actual trial TTV from 200 to 800 ms poststimulus. The mean was then calculated yielding one value, the TTV index. The pseudotrial was subtracted to account to the ongoing spontaneous fluctuations of the neural activity.

stimulus (Wilks' Lambda = 0.972, $F(1,33) = 0.968$, $p = .332$), nor the condition (Wilks' Lambda = 0.924, $F(1,33) = 2.708$, $p = .109$) had significant effects in the broadband. The same was found in the theta band (Wilks' Lambda = 0.984, $F(1,33) = 0.553$, $p = .462$, and (Wilks' Lambda = 0.946, $F(1,33) = 0.1.874$, $p = .180$, respectively)(Sup Mat).

In contrast, in the alpha band there was a significant effect of stimulus (Wilks' Lambda = .815, $F(1,33) = 7.258$, $p = .011$) but not of condition (Wilks' Lambda = 0.999, $F(1,33) = 0.035$, $p = .854$)(Fig. 5B). The same was found for the beta band, with a significant effect of stimulus only (Wilks' Lambda = 0.856, $F(1,33) = 5.556$, $p = .025$, and Wilks' Lambda = 0.996, $F(1,33) = 0.149$, $p = .702$, respectively)(Fig. 5C).

To determine if this significant difference existed only at electrode Pz, an adjacent electrode, POz – still in the centroparietal area – was analyzed with the TTV index in the same two bands. Again, a significant difference between individualized and shared stimuli (Wilks' Lambda = 0.819, $F(1,33) = 7.295$, $p = .011$, and Wilks' Lambda = 0.856, $F(1,33) = 5.556$, $p = .025$) was found in the alpha and beta bands respectively.

Lastly, in the gamma band, neither stimulus (Wilks' Lambda = 0.988, $F(1,33) = 0.412$, $p = .525$) nor condition (Wilks' Lambda = 0.967, $F(1,33) = 1.110$, $p = .300$) had a significant effect on TTV index (Sup Mats).

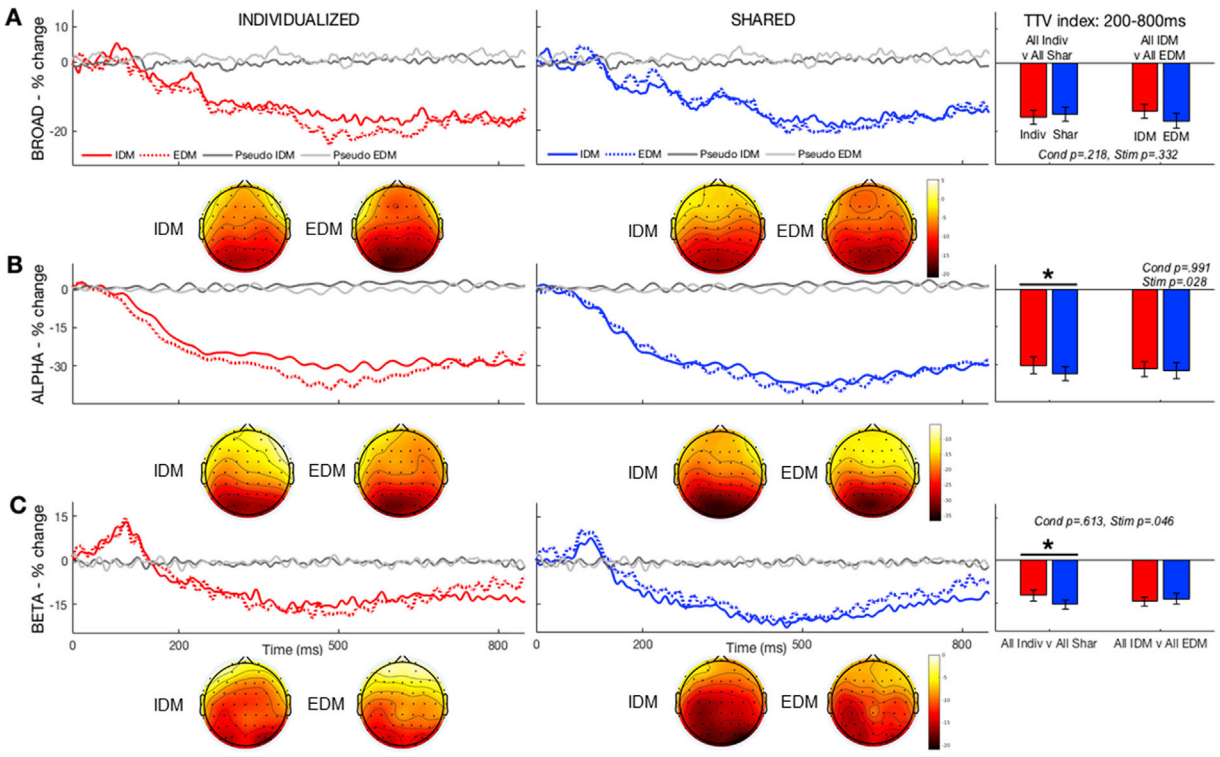

Fig. 5. Trial-to-trial variability (TTV) index for both stimuli and conditions at Pz. **A)** TTV in the broadband (0.5–70 Hz) grouped according to stimulus. Topographical maps for the broadband is below each TTV curve. **B), C)** When the TTV indices for each frequency band were grouped by stimulus (left bars) and condition (right bars), there was found to be a significant effect of stimulus in the alpha (B) and beta (C) bands. *Columns* = stimulus: individualized (left column); shared (center column); bar plots of TTV index values by stimulus and condition (right column). *Rows* = frequency bands: broadband of 0.5–70 Hz (top row); alpha between 8 and 13 Hz (middle row); beta between 13 and 30 Hz (bottom row). Statistics for bar graphs are from a 2 × 2 repeated measures ANOVA. *P*-values are Benjamini-Hochberg corrected for multiple comparisons.

In sum, there was a significant effect of stimulus - individualized vs shared - only in the alpha and beta bands of the TTV index. This features the TTV index as a marker of individuality on the neural level.

3.6. Effect of threshold on TTV index and reaction times

After calculating the above TTV index results, and upon visualization of the data, the effect of threshold on TTV index only in the significant frequency bands was examined. For both alpha and beta, and individualized and shared, a 2 (condition: IDM, EDM) x 2 (stimulus: Individualized, Shared) x 3 (threshold: low, middle, high) repeated measures ANOVA, with between subjects' factor of threshold was performed. As the 2 × 2 statistics were identical to the above values, and the test was done to determine if there was an interaction with the threshold, the statistical values were ignored.

A significant interaction (condition, threshold) was found in the alpha band, ($F(2) = 4.154$, $p = .026$), but not in the beta band ($F(2) = 0.789$, $p = .463$)(Fig. 6A). There was no significant effect of threshold in either band.

Next, to link the TTV index to behavioral measures, correlations were done between the difference of mean reaction times and the difference of TTV indices in alpha and beta bands. The correlation was significant in the beta band ($\rho = 0.461$, $p = .004$) (Fig. 6B) in the IDM condition, but not in the alpha band ($\rho = 0.321$, $p = .099$). Neither the beta ($\rho = -0.119$, $p = .261$) nor the alpha band correlations ($\rho = -0.257$, $p = .162$) were significant in the EDM condition.

In brief, there was a significant effect of threshold on the TTV index in the individualized stimuli of the alpha band, while there was a significant relationship with reaction time in the beta band in the IDM condition. Both findings underline the relevance of TTV for individuality on the behavioral (reaction time) and psychological (threshold) level.

3.7. Lempel-Ziv Complexity prior to and after stimulus onset

After examining the results found in the TTV index related to alpha and beta, and after visualization of the TTV curves, it was decided to measure the complexity of the signal before and after stimulus onset to see if this measure - related to information theory -might suggest a mechanism for our TTV results. Using the LZC measure, 500 ms prior to and after stimulus onset was investigated for complexity (Casali et al., 2013; Ibáñez-Molina et al., 2015; Kalev et al., 2015).

To begin with, we wanted to determine if prestimulus complexity differed from that after the stimulus appeared. Therefore, paired-samples *t*-tests were calculated for all stimuli in both conditions (Fig. 7A). It was found that stimulus onset had a significant effect on complexity for all stimuli (individualized IDM: $t(33) = 9.978$, $p = .002$, shared IDM: $t(33) = 10.821$, $p = .002$, individualized EDM: $t(33) = 9.845$, $p = .002$, shared EDM: $t(33) = 12.354$, $p = .002$). In contrast, the pseudotrials, which functioned here as surrogates for the actual trials, showed no significant difference in either condition ($t(33) = -0.950$, $p = .415$, and $t(33) = -0.848$, $p = .424$, respectively).

After seeing visualisations of the LZC distributions both pre- and poststimulus, a 2 (stimulus: individualized, shared) x 2 (condition: IDM, EDM) repeated measures ANOVA was done to establish if the differences seen visually between complexity before and after onset, and between conditions, were statistically significant (poststimulus complexity minus prestimulus complexity) (Fig. 7B). It was found that there was no significant effect of neither condition (Wilks' Lambda = 0.986, $F(1,33) = 0.433$, $p = .516$) nor stimulus (Wilks' Lambda = 0.988, $F(1,33) = 0.375$, $p = .545$). There was, however, a significant interaction between these two factors (Wilks' Lambda = 0.831, $F(1,33) = 6.087$, $p = .020$).

Because of this significant interaction, two paired-sample *t*-tests were

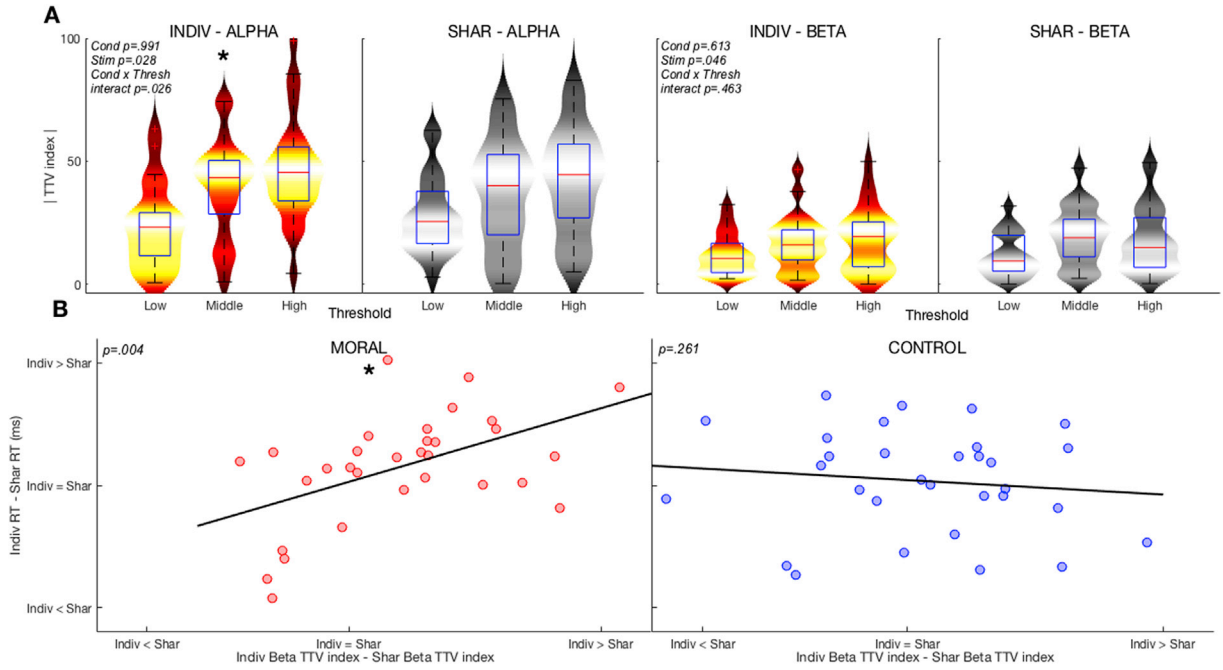

Fig. 6. The effect of threshold on trial-to-trial variability (TTV) index and TTV index correlations with reaction time. **A)** In a $2 \times 2 \times 3$ ANOVA (between subjects' factor is threshold) with three levels (low, middle, high), threshold had a significant interaction on the absolute value of the TTV index in individualized stimuli in the alpha band, but not in the beta band. The TTV index values are grouped according to stimulus, not conditions, for both bands only for reasons of illustration. **B)** In order to focus on the differences related to stimulus, the differences between mean reaction times (individualized minus shared stimuli) and the TTV index in the beta band were correlated. There was a significant correlation in the IDM condition. *P*-values are Benjamini-Hochberg corrected for multiple comparisons.

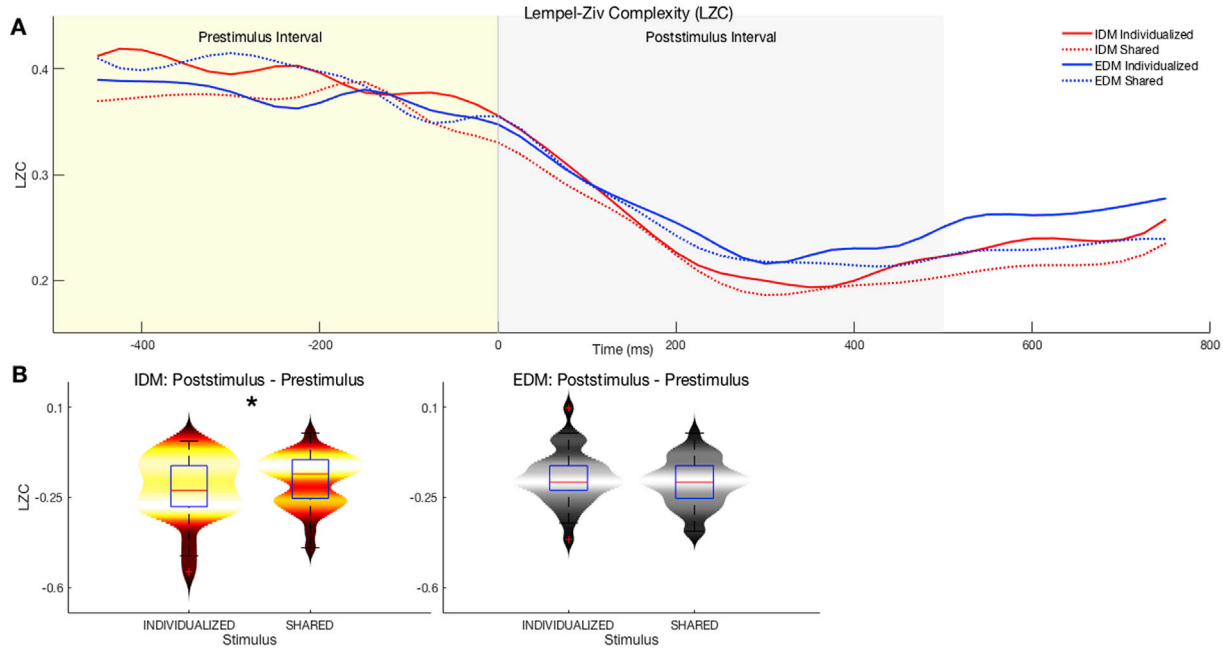

Fig. 7. Lempel-Ziv complexity (LZC) in the prestimulus and poststimulus periods. **A**) To examine complexity as a mechanism for TTV, 500 ms prior to and after stimulus onset were investigated for complexity using the LZC measure. In paired samples *t*-tests, it was found that stimulus onset had a significant effect on complexity in both groups of stimuli and conditions. In contrast, there was no significant difference in the pseudotrials, which acted as surrogates. The time-resolved LZC seen here was computed for visualization only using a window of 500 ms, overlap of 90%, and step of 50 ms. Line curves were smoothed in MATLAB using the function *spline*. **B)** Two paired-samples *t*-tests was conducted comparing the difference in LZC related to stimulus onset between the individualized and shared stimuli in both conditions. There was a significant effect of stimulus in the IDM condition, but not in the EDM condition. *P*-values are Benjamini-Hochberg FDR corrected for multiple comparisons.

conducted on these LZC difference values, between the individualized and shared stimuli (Fig. 7B). A significant effect of stimulus ($t(33) = -2.381$, $p = .048$) was found in the IDM condition, not in the EDM condition ($t(33) = 0.934$, $p = .357$).

Finally, to determine if prestimulus LZC was related to poststimulus TTV in alpha and beta, correlations were calculated. A significant correlation was found in the alpha band only (Fig. 8). Specifically, there was a significant correlation in the individualized stimuli ($\rho = 0.477$,

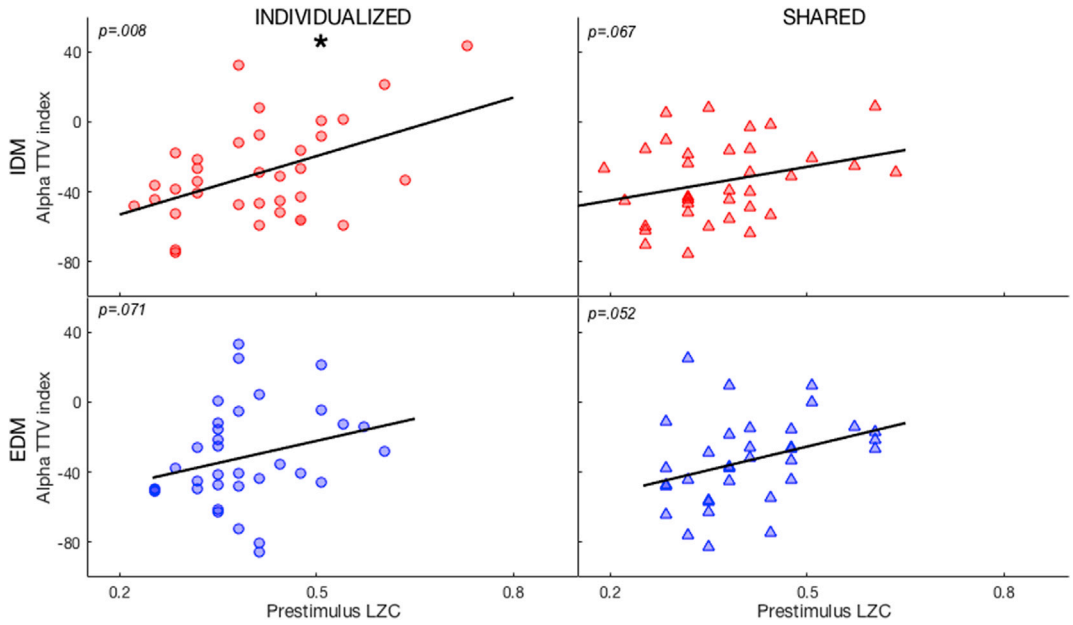

Fig. 8. Prestimulus Lempel-Ziv complexity (LZC) correlates with alpha TTV index. **A**) To determine the relationship between prestimulus LZC on TTV index in alpha, one-tailed Pearson correlations were calculated. Significant correlations were found in the individualized stimuli in the IDM condition, not the shared. Neither the individualized nor the shared stimuli had significant correlations in the EDM condition. *P*-values are Benjamini-Hochberg FDR corrected for multiple comparisons.

$p = .008$) of the IDM condition and not the shared stimuli ($\rho = 0.287$, $p = .067$). Neither the individualized ($\rho = 0.257$, $p = .071$) nor the shared ($\rho = 0.344$, $p = .052$) stimuli had significant correlations in the EDM condition.

All together, these findings show that complexity decreased after stimulus onset in all stimuli and conditions, however this pre-to post-stimulus decrease was significantly different between individualized and shared stimuli in the IDM condition. In addition, a significant relationship between prestimulus complexity and TTV index in the alpha band was found in the individualized stimuli of the IDM condition. These findings suggest that pre-stimulus complexity mediates the individual features of post-stimulus TTV.

3.8. eLORETA source localization correlations with alpha and beta TTV index

To support our correlations between the alpha TTV index and prestimulus LZC and beta TTV index and reaction time, we performed correlations between these TTV indices and eLORETA source activity in the visual cortices.

There was a significant correlation between the visual cortices eLORETA activity from the individualized stimuli and the TTV index in the beta band ($\rho = -.421$, $p = .032$) in the IDM condition (Table 1). The correlations for the shared IDM ($\rho = -0.178$, $p = .264$), individualized EDM ($\rho = -0.154$, $p = .264$), and shared EDM ($\rho = -0.116$, $p = .264$) were not found to be significant. None of the correlations in the alpha band were significant ($p = .104$, $p = .206$, $p = .403$, and $p = .212$).

Finally, to determine if the significant correlation was only in the visual cortices, the same analysis was performed in the premotor cortex, the posterior cingulate cortex and the inferior parietal lobules as control regions. For activity in these ROIs, none of the correlations were significant: premotor cortex - $p = .168$, $p = .435$, $p = .340$, and $p = .340$; posterior cingulate cortex - $p = .094$, $p = .418$, $p = .456$, and $p = .476$; inferior parietal lobules - $p = .094$, $p = .426$, $p = .217$, and $p = .268$, respectively.

Together, these eLORETA source localization findings show a correlation between the beta TTV index and individualized stimuli, and that this activity was specific to the visual cortex.

Table 1
Significance values for correlation between eLORETA activity (0–200 ms) and beta TTV index.

CORTICAL AREA	INDIV. IDM	INDIV. EDM	SHAR. IDM	SHAR. EDM
VISUAL CORTEX *(BA 17, 18)*	.032	.264	.264	.264
PREMOTOR CORTEX *(BA 6)*	.168	.340	.435	.340
POSTERIOR CINGULATE CORTEX *(BA 29/30, 23/31)*	.094	.456	.418	.476
INFERIOR PARIETAL LOBULES *(BA 39,40)*	.094	.217	.426	.268

ALL SIGNIFICANCE VALUES ARE BENJAMINI-HOCHBERG FALSE DISCOVERY RATE CORRECTED.

4. Discussion

We investigated the behavioral relevance and neuronal mechanism of TTV. Applying a specific paradigm for testing internally-guided decision making, we observed that TTV, specifically in the alpha and beta bands, showed significant differences between individualized and shared stimuli in specifically IDM (as distinguished from EDM). This finding suggests that TTV can be considered a marker of the individual specifics of individual neural activity and its manifestation on psychological and behavioral levels.

Crucially, we show that TTV for individualized stimuli is related to prestimulus complexity, as measured by LZC. This suggests that individualized TTV quenching is related to a reduction of prestimulus information complexity which, as our data suggest, mediates the individual features of post-stimulus TTV. Together, our data show for the first time that TTV quenching is a highly individualized neural marker and is mediated by prestimulus information complexity.

These results carry major implications for our understanding of the behavioral relevance and neuronal mechanisms of how the more internally-based spontaneous activity, specifically prestimulus activity, interacts with external stimuli as during stimulus-induced activity.

4.1. TTV as neural marker of individuality

Arazi et al. (2017b) demonstrated that TTV remains stable within one

participant across tasks as well as over time. These results suggest that TTV is a trait marker of the individual participant and distinct from others. If this is the case and TTV is indeed a neural trait marker of individuality, one would expect that TTV responds to the individual rather than shared features of stimuli in perceptual or cognitive paradigms. To test this, we applied a novel study design of an IDM task. This allowed us to compare directly individualized stimuli to shared by individualizing the threshold of our paradigm while simultaneously controlling for task-related effects (two conditions, IDM and EDM). As expected, our behavioral data shows that participants differed in their respective thresholds as indexed by the ratios related to the IDM dilemma presented.

The neural effects of these individualized thresholds, which manifested in individualized stimuli, were then compared with those of stimuli presented to all participants. As expected, this led to significant differences in ERP (N100 and P300), ERSP (alpha band power), and ITC (delta and theta band) between individualized and shared stimuli. Notably, these differences could not be traced to task-related aspects; there were no significant differences between IDM and EDM in these measures. Our results are well in accordance with others showing analogous effects of individualized stimuli on ERP, ERSP, ITC and other measures (Houben and Wiers, 2007; Qin et al., 2008; Kessler et al., 2011, 2017; Wiswede et al., 2014; Bai et al., 2016).

As it was the main target of our study, it was of great importance that we demonstrated significant differences in TTV between individualized and shared stimuli in the alpha and beta frequency bands, specifically. Though our examination of TTV is well in accordance with the various studies in EEG/MEG (He and Zempel, 2013; Schurger et al., 2015; Arazi et al., 2017a) and fMRI (He, 2013; Ferri et al., 2015; Huang et al., 2017b, 2018), the present results add two important innovations to the growing TTV literature, first TTV is a marker of neural individualization and secondly, post-stimulus TTV is mediated by pre-stimulus information complexity.

We demonstrate that TTV effects are related to the individual neural response to a stimulus. While previous studies showed interindividual differences in TTV (Ferri et al., 2015; Arazi et al., 2017a, 2017b), here we tested the hypothesis of TTV as an individual neural marker by comparing individualized and shared stimuli directly. This approach yielded significant differences in TTV related to stimulus, specifically in the alpha and beta bands (other bands showed TTV but no differences between stimuli). In addition, the eLORETA results supported this finding with a significant correlation between the visual cortex and TTV in the beta band only in individualized stimuli.

Furthermore, the significant correlations in the individualized stimuli only in the IDM condition suggests that an aspect of the stimulus interacts with the condition. It may be that individualization is relevant only in some contexts for some measures as they require more internally oriented criteria (Nakao et al., 2012). Such findings are consistent with literature related to IDM – preference based – and EDM – objective response – decision-making (Nakao et al., 2010, 2012, 2016) as in IDM the response depends on the participants' own internal criteria as mediated by their internal pre-stimulus activity, specifically its variance and complexity. Our findings imply that in certain measures, the context of the stimulus (IDM or EDM) has a further impact on the stimulus induced activity as may occur in IDM. Further disambiguation of this, however, is required.

The special role of individualized TTV in the beta band is further supported by our finding of a significant correlation between the beta TTV index in the individualized stimuli and reaction time. Together, these findings suggest that 1) TTV represents a neural marker of individuality, and that 2) such 'neural individualization' is processed in the alpha and beta frequency bands specifically. As the need for obtaining neural markers of individualization grows in both basic and clinical neuroscience (Braver et al., 2010; Reineberg et al., 2015; Friedman and Miyake, 2016; Jang et al., 2017; Seghier and Price, 2018), we here suggest that TTV in the alpha and beta bands can provide a marker of neural individualization.

4.2. TTV is mediated by changes in information complexity from pre-to post-stimulus periods

Previous data at both the cellular (Kisley and Gerstein, 1999; Curto et al., 2009; Schurger et al., 2010; Pachitariu et al., 2015) and regional level (He, 2013; Schurger et al., 2015; Huang et al., 2017b) suggest that prestimulus activity amplitude or variance are central in mediating poststimulus TTV quenching. Despite these important results, the exact feature of prestimulus activity which mediates poststimulus TTV quenching remains unclear.

We therefore asked the following question: is poststimulus TTV also mediated by the information complexity of prestimulus activity? In a first step, we investigated the complexity - through the measurement of LZC - of both prestimulus and poststimulus activity in two 500 ms intervals. LZC, and thus complexity, was significant higher in the prestimulus period in both individualized and shared stimuli. While new by itself (Ponce-Alvarez et al., 2015), this higher prestimulus complexity is in accordance with the above cited findings related to increased prestimulus activity levels or variance preceding poststimulus TTV. Together, both suggest that the higher amplitude/variance prior to stimulus onset represents a higher information complexity, which decreases after the stimulus is presented. Such a stimulus-related difference in information complexity appears to be a basic, general neural mechanism since no differences between conditions (IDM and EDM) were found.

Remarkably, we found that these high prestimulus complexity levels were related to TTV in the alpha band in individualized stimuli of the IDM condition. In contrast, no such correlation was found in shared stimuli or in EDM. These findings suggest that TTV in the alpha band in response to individualized stimuli is closely related to prestimulus information complexity. Given that in the poststimulus period both TTV and complexity were quenched - reduced compared to prestimulus levels - we suggest that a reduction in information complexity and variability during the poststimulus period are central to mediating the individual's neural response to stimuli. It has previously been shown that resting state activity interacts with task-evoked activity (Northoff et al., 2007, 2010; He, 2013; Huang et al., 2017b), and that activity during IDM overlaps with the default mode network (DMN) (Northoff et al., 2006; Nakao et al., 2012). From these findings, it has been inferred that IDM is heavily influenced by the brain's intrinsic activity (Nakao et al., 2012). Our prestimulus complexity and individualized IDM TTV findings are strongly guided by the brain's intrinsic activity - its pre-stimulus activity - which is consistent with this view, however further work is required to support this.

Broadly, our data indicate, albeit tentatively, that spontaneous prestimulus activity and stimulus-induced activity is both nonadditive (He, 2013; Huang et al., 2017b, 2018) and individualized. If an interaction were additive, one would observe increases in both TTV and complexity; following the law of variance (He, 2013), the contributions of both spontaneous activity and stimulus are added during stimulus-induced activity. Since the opposite results were found with post-stimulus decreases in both TTV and complexity, our data strongly support a nonadditive (He, 2013; Huang et al., 2017b, 2018), rather than additive (Arieli et al., 1996; Fox et al., 2006; Becker et al., 2011) model of rest-stimulus interaction. Taken together with our observation of TTV as a marker of neural individualization, we suppose that nonadditive rest-stimulus interaction is by itself individualized. This is especially supported by our finding that TTV only from individualized (but not shared) stimuli correlated with complexity (and reaction time on a behavioral level).

The mechanism of TTV reduction has previously been related to the disambiguation or clarification of stimuli which allows for better information processing in the cortex (Monier et al., 2003; Finn et al., 2007; Churchland et al., 2010; White et al., 2012). Furthermore, modeling studies have shown that variability reduction can occur from recurrent network processing; in a multi-attractor system, the stimulus presentation can stabilize one attractor thereby suppressing the transition to other

attractors (Deco and Hugues, 2012; Mazzucato et al., 2015). This stabilization of one attractor reduces net neural variability by increasing the neural orderliness (Deco and Hugues, 2012; Mazzucato et al., 2015). Spike train data has also shown a similar variability reduction due to increased regularity of spike train activity (Deco and Hugues, 2012). This increased uniformity then leads to a decrease in the transfer of information - according to Shannon information theory (Shannon, 1948; Gershenson and Fernandez, 2012) – as reduced variability is associated with more structure, and hence with increased predictability in data (Gershenson and Fernandez, 2012).

This decreasing transfer of information and clarification of stimuli may be evident in the reduced complexity after stimulus onset shown here. The question, then, is do individualized stimuli reduce the neural variability less than non-individualized stimuli because of their decreased regularization of the activity? How is this related to the prestimulus spontaneous activity since reduced quenching is less deviation from resting state activity? Could early life experiences (Duncan et al., 2015) and genetic influences (Hensch, 2005) be large contributors to these mechanisms, as a recent study suggested (Arazi et al., 2017b)? This hypothesis is tentative, at best, and requires testing in future studies.

4.3. Methodological limitations

One may argue that TTV already includes prestimulus intervals indirectly, rendering calculations of both poststimulus TTV and prestimulus complexity dependent variables rather than independent. This, in turn, would render their correlation spurious. While indeed TTV is calculated in most studies in reference to stimulus onset (Ferri et al., 2015; Schurger et al., 2015; Arazi et al., 2017a, 2017b, Huang et al., 2017b, 2018), we here introduced a novel method to avoid such dependence between TTV and prestimulus measures.

We adopted the method of pseudotrials (Huang et al., 2017b), or trials when a stimulus is absent (Dinstein et al., 2015), by inserting a pseudo-stimulus into the intertrial intervals. These pseudotrials had a buffer which ensured they remained independent of the prestimulus period and actual trial offset. We then calculated TTV for such pseudotrials and subtracted them from the actual trial TTV during the poststimulus period. Such calculation of TTV thus allowed for its independence from the prestimulus period, including its manifestation at stimulus onset. This allowed us to calculate prestimulus LZC independent of poststimulus TTV which, in turn, made the correlation possible as both were independent variables.

Another methodological issue consists in the lack of control for threshold proximity. The two individualized stimuli were also the ones near the threshold since the threshold defined the individualization. Presenting the participants with two stimuli that were 1) near the threshold in the same degree as the individualized stimuli, but 2) not individualized, would have been optimal controls for the proximity to the threshold. Therefore, the comparison to the individualized stimuli were stimuli presented to all participants. Their distance from the threshold (if threshold was 5:7, the shared stimuli were 1:11 and 10:2), however, was not equal.

The final study limitation relates to a lack of eye-tracking during the EEG session. Two related papers (Arazi et al., 2017a, 2017b) employed an eye-tracker while conducting their EEG study. Though we did not use this technology, we controlled for eye movements in several ways. During the study itself, the stimuli included a fixation cross at the center, and participants were seated 55–60 cm away from a 34.3×26.7 cm computer screen. This was done to minimize eye movements and the visual angle. We also used additional bipolar electrodes, placed at the outer canthi of the eyes and above and below the left eye, to measure eye movements and aid in artifact rejection during EEG preprocessing. When the data were visually inspected, all trials with blinks in the baseline period (−200 ms to stimulus onset) were removed. Finally, to remove blinks and saccades in the remaining EEG data, independent component analysis (ICA) and the Multiple Artifact Rejection Algorithm (MARA) (Winkler et al., 2011, 2014) of EEGLAB (Delorme and Makeig, 2004), which standardized the artifact rejection process, were used.

5. Conclusion

The spontaneous activity of the brain interacts with task-evoked activity; however, the exact mechanisms of this interaction including its individually-specific nature remain unclear. We here investigated the individual behavioral relevance and neural basis of one neural marker of rest-stimulus interaction, namely trial-to-trial variability (TTV), during internally-guided decision making. As in previous studies at both the cellular and regional levels, we observed poststimulus TTV quenching which, in an extension to this previous work, was found in alpha and beta bands related to specifically individualized, but not shared, stimuli. We thus consider TTV in the alpha and beta band a marker of neural individualization. Notably, we demonstrated that TTV in the alpha band was related to prestimulus information complexity, as measured by Lempel-Ziv Complexity (LZC). Indexing internal neural activity yet unrelated to the external stimulus, pre-stimulus complexity may thus mediate the individually-specific features of TTV during the post-stimulus period on both neural and psychological levels.

Together, we demonstrate, for the first time, that poststimulus TTV quenching is a marker of 'neural individualization' which is mediated by prestimulus information complexity. Broadly, considering TTV as an internally-based marker of rest-stimulus interaction, these findings suggest that the interaction between the purely internal spontaneous and internal-external stimulus-induced activity is both nonadditive and individualized.

Conflicts of interest

No known conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.02.070.

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