



The individuality index: a measure to quantify the degree of inter-individual, spatial variability in intra-cerebral brain electric and metabolic activity

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Abstract

Contemporary neuroscience research primarily focuses on the identification of brain activation patterns commonly deviant across participant groups or experimental conditions. This approach inherently underestimates potentially meaningful intra- and inter-individual variability present in brain physiological measures. We propose a parameter referred to as ‘individuality index (II)’ that takes individual variability into account. It quantifies the degree of individual variance of brain activation patterns for different brain regions and participants. IIs can be computed based on intra-cerebral source strength values such as the ones derived from the exact low resolution electromagnetic tomography source localization software. We exemplarily estimated IIs for simulated datasets. Our results illustrate how IIs are affected by different spatial activation patterns across participants and quantify their distributional properties. They suggest that the proposed indices can meaningfully quantify inter- and intra-individuality of brain activation patterns. Their application to realistic datasets will allow the identification of (1) those brain regions that show particularly heterogeneous activation patterns, the contribution of which is particularly likely to be underestimated by conventional group statistics, (2) those brain regions that can alternatively be recruited by different participants for the same tasks, and (3) their associations with potentially decisive behavioral variables such as individually applied mental strategy.

Keywords Individuality-index · Individuality · Spatial variability · Brain activation patterns

Introduction

Contemporary neuroscience research primarily focuses on the identification of common brain activation patterns across participants that can be statistically distinguished between conditions (e.g., resting vs. task) and/or participant groups (e.g., patients vs. controls). Via group

statistics, those brain regions are identified that “on average” are more strongly activated in one condition versus another or in one group of individuals versus another. This approach, however, largely neglects the considerable degree of inter- and intra- individual variability most commonly observed during any condition and in any group in measures of brain activation (e.g., Houdé and Tsourio-Mazoyer 2003; Fehr et al. 2011; Fehr 2013).

This neglect may have detrimental effects on the field. It may, at least in part, account for the largely dissatisfactory levels of intra- and inter-trial reliability (Thirion et al. 2007; McGonigle 2012; Fehr et al. 2014) and have introduced a bias towards asserting the involvement of more homogeneously structured brain regions in a brain function or disease whilst underestimating the potential individual importance of more heterogeneously activated and/or structured brain regions. The question arises what the cause of this widely reported inter-individual and intra-individual variability might be and how these causes can be accounted

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for in contemporary statistical analyses (McGonigle 2012; Button et al. 2013).

Joyce et al. (2010) proposed a method that identifies central networks and nodes of individually different leverage impact (i.e., functional connectivity between particular nodes and corresponding target nodes that do not get only few input from other nodes) based on individual functional neuroimaging data. To identify their most representative data set in their sample, they quantified the similarity between individuals by Jaccard indices (e.g., Tan et al. 2005). Principally, Jaccard-similarity quantifies the similarity of two binary data vectors by dividing the number of 1-1-matches by the total number of bits minus the number of 0-0-matches, whereas another similarity measure, the Hamming distance, just accounts for the number of different bits between the two binary data vectors (Hamming 1950). Thus, estimating similarity on the basis of binary data structures is not a new idea. Casali et al. (2013) applied the Lempel–Ziv complexity approach (see also Schartner et al. 2015) to determine the “amount of nonredundant information” in binarized Minimum-Norm source data based on TMS-induced EEG brain activity. They found different brain functional complexities for different conscious levels in their study participants. The approach introduced in the present schrift can be applied to single binary bit (i.e., single voxel) or matrix (i.e., any voxel cluster) data structures.

For cognitive neuroscience, two major causes of inter- and intra- individual differences were proposed. Different participants or the same participants across time (1) may apply different mental strategies to solve the same task (Fehr et al. 2011; Fehr 2013; Milz et al. 2016a, b) and/or (2) they may recruit regionally distinct brain regions to apply the same or similar mental strategies.

The former point is illustrated in studies that investigated inter-individual and intra-individual differences in applied modality of thinking. Modality-related sensory and motor processing is carried out, to a large degree, by homogenously structured topographically organized brain regions such as the primary visual, auditory, somatosensory, and motor cortices. However, for the same task, different individuals favor more object-visual, spatial-visual, or verbal mental strategies, which reflects in the activation of the respective cortices (Milz et al. 2016a, b). Latter point is of crucial significance to the field of functional neuroimaging as a whole. The same functional process may be exhibited by different brain regions in different individuals. This may particularly be the case within associative cortices that exhibit higher order processing, are not topographically organized, and thus might considerably vary in functional structure across participants (Fehr 2013). On the other side, there are also neural correlates that appear to be rather idiosyncratic and can

even be related to particular individuals in a reliable way (e.g., De Vicco Fallani et al. 2011; Pirondini et al. 2017).

The extent to which inter- and intra-individual differences can be accounted for by different mental strategies and brain functional structures remains speculative until the degree of functional homo- and heterogeneity of different brain regions can be quantified and statistically evaluated optionally at single individual and single voxel levels. For this reason, we propose a measure to quantify the degree of functional heterogeneity in particular brain regions, the ‘individuality index’ (= II). The II estimates the degree of individual variance of brain activation pattern for any given region of interest. It provides a simple approach, by which for any given brain region and any given individual, the dissimilarity of the activation pattern of this individual with all other individuals in the sample is computed. These individual values can then be averaged and illustrated across individuals (alternatively, geometric means, medians, or weighted averages might also be used to quantify central characteristics of respective regions of interest). They can be used to identify regional differences in the task-condition-related or group-related amount of inter-individuality, and they can be used to assess relationships between individual mental strategy profiles and external variables to assess the involvement of different brain regions in different thinking modalities (e.g., executive, spatial, visual, object-related, and other kinds of cognitive processing styles) and idiosyncratic memory-recruitment (cmp. Fehr 2013; Fuster 2006, 2009).

The present work describes the different types of functional neuroimaging data that the proposed II can meaningfully be applied to. It illustrates its computation, possible result patterns, and distributional properties based on a simulated dataset. Furthermore, it discusses potential applications in the empirical sciences on idiosyncratic spatio-temporal, functional neural correlates of complex mental processing.

Methods

Pre-processing

The individuality index (II) can be computed based on any spatially-resolved neuroimaging source file including data from metabolic activity derived from functional Magnetic Resonance Imaging (fMRI) and source-localized data from brain electric activity as derived from event-related potentials (ERP) or continuous electroencephalography recordings (EEG).

However, its computation requires binary voxel-values that indicate for each brain anatomic voxel, whether it is activated (= 1) or not (= 0). Whereas individual fMRI-

activation patterns are already available in this format, and thus require no additional preprocessing, a binarization procedure must be applied to continuous electric source strength data that are available on an interval scale such as the intra-cortical current density values derived from EEG/ERP measures via exact low resolution electromagnetic tomography (eLORETA).

For EEG/ERP measures a number of approaches can be applied to retrieve binary activation values (e.g., Casali et al. 2013; Schartner et al. 2015). For ERP data, source strength values between a baseline and post-stimulus time (signal-line) interval can also be compared for each voxel via (1) one-sample t-tests that compare each signal-line timeframe to mean baseline activity or (2) unpaired t-tests that compare mean signal-line activity in time-windows of interest (TOIs) to mean baseline activity. For EEG data, (1) mean EEG frequency-band wise source strength values can be compared between a baseline condition and a condition of interest via paired t-tests or (2) for each timeframe, voxel-wise source strength vectors (three components) can be computed and tested for absolute activation against zero mean values (Pascual-Marqui et al. 2014).

For the present study, a simulated dataset was used that already contained binary activation values of regional, intra-cerebral source activation. Thus, no pre-processing for binarization was required in the present case.

Simulated data

There are different ways to simulate appropriate data for the illustration of the here proposed methodological approach. The simulated dataset in the present work was generated via a Matlab[®] script (V6.5). The respective script can be adapted in many ways. The here used version demands as input the specification of the number of individuals, for which source distribution data is to be simulated, the centers of any number of voxel clusters (for the appliance for this particular version of the script any MNI-coordinate in the LORETA-space of 6239 voxel-coordinates can be selected), the cluster dimensions (can be set individually for each cluster), and a general percentage weighting parameter (between 0 and 1) that more or less reduces the percentage values generated for each voxel-value in a particular cluster.

Based on these parameters, for each individual, a multi-cluster distribution of continuous spatial activation values was computed. The retrieved voxel-wise values were binarized by setting voxel-values larger than or equal to .5, to 1 and voxel-values lower than .5, to 0. For a given cluster, the probability for a voxel to be activated decreases linearly towards the edges of the defined cluster dimensions (center voxel keeps 100% of the random number

generated; edge-voxels are weighted 60% of that same number).

Computation of the individuality index (II)

The majority of functional neuroimaging investigations on complex mental processes is arguably still at a prescientific and exploratory hypothesis-generating stage. This shows particularly with regard to the substantial neglect of type-2-errors (cmp., Lieberman and Cunningham 2009; Fehr 2013). For this reason, we propose to compute the individuality index (II) based on an exploratory, data-driven strategy.

This strategy considers the ambiguity that for any brain area that shows a lack of activation in all individuals, we do not know whether it was indeed not activated in any individual or whether it was activated but our method of recording was not sensitive enough to detect this activation. For this reason, the proposed approach only considers those areas to be inactivated in any given individual if it was detected to be activated in at least one individual of the sample. Areas that do not satisfy this criterion are ignored in subsequent calculations.

The individuality index (II) quantifies the individuality of each participant in a respective spatial, neuronal unit (e.g., voxel of interest = VOI). It is computed as follows:

Suppose there are N individuals in the sample, $i = 1, \dots, N$. Fix a VOI “Voxel of Interest”. The data is just a vector $v = (v_1, \dots, v_N)$ with $v_i = 1$, if there was activation and $v_i = 0$, if not, for each $i = 1, \dots, N$. The “individuality index” for this VOI and a fixed participant i is the fraction of the other participants, which differ from i at that VOI,

$$II_i(v) = \frac{1}{N-1} \sum_{j \neq i} (1 - \delta_{ij}(v))$$

where $\delta_{ij}(v)$ is Kronecker’s delta, that is,

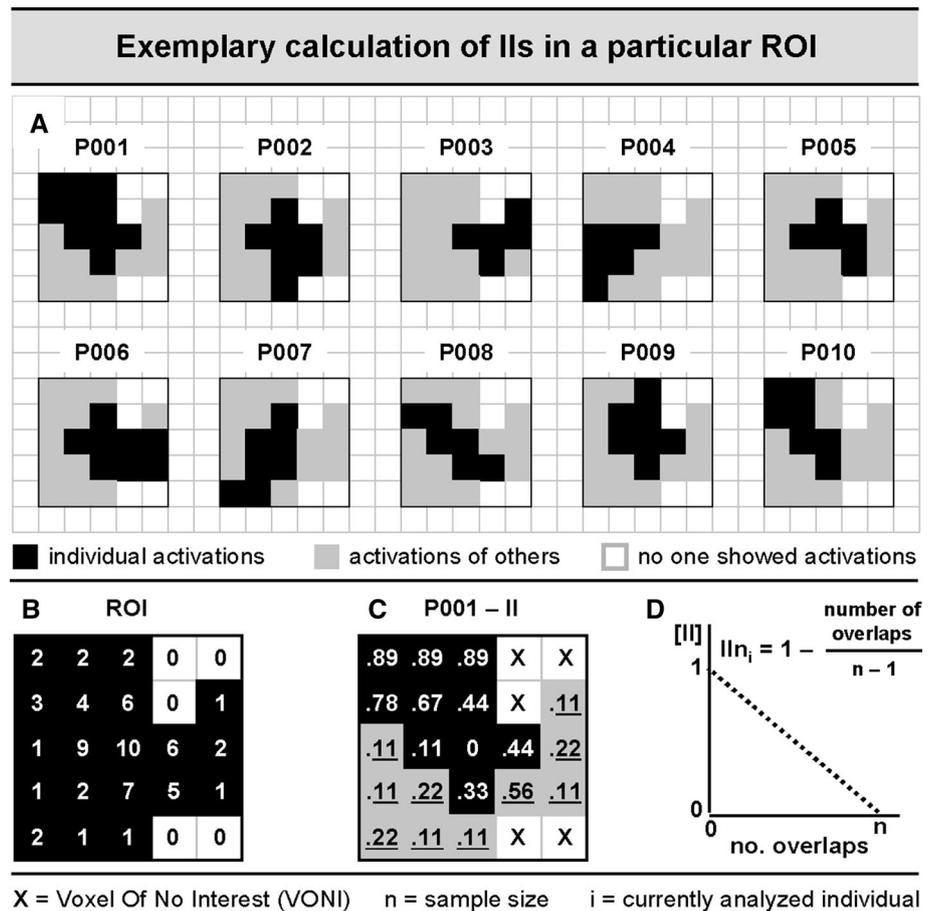
$$\delta_{ij}(v) = \begin{cases} 1 & \text{if } v_i = v_j \\ 0 & \text{if } v_i \neq v_j \end{cases}$$

Let $O(v) = \sum_{j=1}^N v_j$ be the number of individuals for which there was activation. Then,

$$II_i(v) = 1 - \frac{1}{N-1} \sum_{j \neq i} \delta_{ij}(v) = \begin{cases} 1 - \frac{O(v)-1}{N-1} & \text{if } v_i = v_j \\ \frac{O(v)-1}{N-1} & \text{if } v_i \neq v_j \end{cases}$$

So, for a fixed VOI, the vector of II s is just a rescaling of the vector of 0 s and 1 s, which cannot and does not contain any new information with respect to the data in v . For example, if $v = (1, 1, 0, 0, 1, 1)$, then the vector of $II_i(v)$ is just $(\frac{2}{5}, \frac{2}{5}, \frac{4}{5}, \frac{4}{5}, \frac{2}{5}, \frac{2}{5})$. See Sect. 3.1, Fig. 1 for an illustrative example.

Fig. 1 **a** Exemplary calculation of voxel-wise II-values; **b** number of individuals overlapping in activation (voxel wise); **c** voxel wise IIs for case P001; **d** relationship between inter-individual activation-overlap and II (for one voxel)



IIs of regions of interests that comprise multiple voxels can be computed for example by averaging voxel-wise IIs. However, it remains unclear so far, whether means over ROIs provide the best approach to estimate ROI-related IIs; geometric means, medians, or weighted averages might provide a better basis to determine the individual character of a given ROI. This has to be shown in subsequent studies on physiological data.

Alternatively, ROI-wise IIs can be computed by binarizing ROI activities (i.e., evaluating the activity of a given ROI to 1, if the number of voxels activated within the ROI exceed a particular threshold and to 0, if it does not) to then determine correspondence vectors-based ROI-level activity comparisons directly. The latter approach allows to add additional smoothing to the data to account for low spatial specificity such as commonly observed in EEG-derived source strength data.

Results

Illustration of II-calculation procedures step-by-step

The calculation procedure of the individuality index (II) is illustrated in Fig. 1. For ten notional individuals (P001 to P010) in one notional brain slice (2-dimensional area), individual binary activation patterns across 25 voxels (5 by 5 matrix) were defined (Fig. 1a). The voxel-wise IIs that result from the respective dataset for P001 (= an exemplary individual of interest = IOI) are depicted in Fig. 1b. Figure 1c schematically illustrates the relationship between VOI-related II-values and the respective number of overlaps in a given sample of n individuals.

The IIs in Fig. 1b. illustrate how that individuals' II score is maximal in those voxels that they activate almost uniquely compared to other individuals (e.g., row 1, columns 1–3) and minimal in those voxels that they activate in common with most other individuals (e.g., row 3, column 2). The same pattern applies to rather unique (e.g., row 4, column 4) and common (e.g., row 3–4, column 1) deactivations in voxels.

We note that voxels that were not activated by any individual in the sample were ignored for II calculation and the respective voxels marked by an X (voxel of no interest = VONI).

Simulated data: nine virtual ‘individuals’

Simulation of nine data sets (see Sect. 2.2 for details on the procedure) with two activation clusters each (one left hemispheric = LH and one right hemispheric = RH) led to individual activation patterns comparable to realistic data from fMRI first level analysis or eLORETA data as outlined in Sect. 2.1 (see Table 1 for regional individual voxel distribution).

Figure 2b illustrates binary activation in an exemplary horizontal slice of each of the nine simulated data sets P1 to P9. Two clusters of activation distributed bilaterally in inferior and middle frontal areas can be seen. Figure 2a (left part) shows the relative overlap of individual activations, the right part illustrates mean II-values. In Fig. 2c, voxel-wise II-values are illustrated for each simulated, individual data set P1 to P9. Patterns of individual voxel-wise IIs suggest a quite heterogeneous picture across individuals.

In Table 2, mean regional IIs (left part) and mean regional distributions of these IIs (right part) for each individual and for the respective left and right hemispheric ROI-voxel-clusters were listed accordingly. Overall means across individuals and respective standard deviations were illustrated in Fig. 3. For the simulated data presented here, both mean regional II-values across individuals and intra-individual distributions (standard deviations, SD) of regional II-values did not show any significant laterality effect (paired *T* Test between left and right hemispheric ROIs: $t = 1.41$; $df = 8$; $p = .197$, $n = 9$; see Tab. 2 for means and SDs). If observed in real, empirical datasets such regional differences and selective correlations between regional IIs and non-physiological variables would provide valuable information on HOW a brain region is recruited into execute particular complex mental processes.

Discussion

The introduced algorithm for the quantification of functional, brain regional individuality (i.e., the Individuality Index, II) is characterized by its simplicity and efficiency. It is based on binary activation values derived from each individual separately (in this work, a simulated data set) to take into account that neurophysiological data are frequently not normally-distributed and value-distributions show large individual variations (e.g., McGonigle 2012; Holmes and Friston 1998; Fehr et al. 2003; Fehr 2013). Binarizing functional brain activation data (see also Casali et al. 2013; Schartner et al. 2015) on the individual level, allows the analyses of respective spatial distribution and/or dynamic aspects of brain activation, without considering interindividual distributional characteristics of the underlying physiological substrate (i.e., blood oxygen level dependent measures by fMRI, metabolic measures by PET, EEG or MEG-data).

The respectively computed IIs can be compared between voxels of interest (VOIs), regions of interest (ROIs), and groups of interest (GOIs) to determine brain-regional specificities in processing-individuality. VOI-based analyses allow the high-resolution exploration, ROI-based analyses the medium- to low-resolution investigation of regional and hemispheric individuality differences. The latter can be constructed by combining voxels of anatomical or functional sub-regions (e.g. Brodmann areas, hetero-modal association versus topographically organized cortices; cmp. Fuster 2006, 2009).

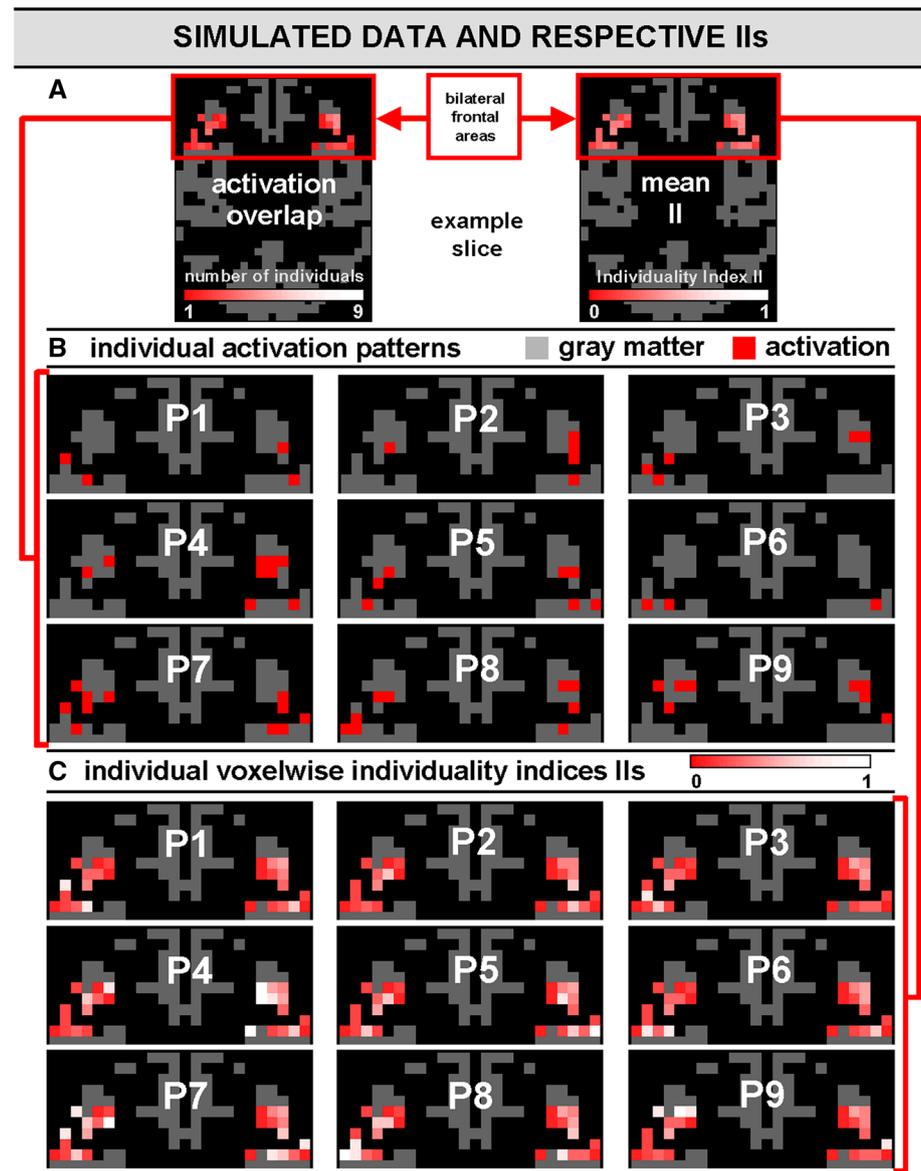
As in real neurophysiological measures, the data simulated here showed considerable distribution of values across individual data sets. Those inter-individual distributions were discussed to provide a valuable source of information about idiosyncratic properties of particular kinds of brain regions (e.g., McGonigle 2012) such as topographic and hetero-modal association cortices (Fuster 2006, 2009). Correlations with non-physiological variables (e.g., measures of individual mental strategies, training success to gain expertise, age, trait variables and many more) provide a way to sufficiently explore the relevance

Table 1 Number of regionally activated voxels ($5 \times 5 \times 5$ mm voxel dimension) in nine virtually simulated individual data sets

Individual, regional number of activated voxels in simulated data sets																		
Anatomical region	Left hemispheric									Right hemispheric								
	P01	P02	P03	P04	P05	P06	P07	P08	P09	P01	P02	P03	P04	P05	P06	P07	P08	P09
MFG	1	1	2	0	1	2	3	3	1	1	1	1	1	0	3	1	3	1
IFG	16	18	18	12	18	8	13	8	11	13	10	14	18	20	8	7	9	18

MFG middle frontal gyrus; IFG inferior frontal gyrus

Fig. 2 **a** left panel: The activation overlap across nine simulated data sets for an exemplary slice; a right panel: the mean voxel-wise IIs across the simulated data sets; **b** all nine simulated data sets; **c** Individual voxel-wise IIs. See Tab. 2 for numerical information of the whole cluster of ROIs



of particular ROIs and sub-ROIs for the processing of particular complex mental operations (e.g., Fehr 2008, 2013). An additional important aspect that has to be considered in particular is the trial-by-trial consistency of both behavioural and physiological data. Reliability in behavioural and physiological measurements can be modulated by a broad variety of contentual and methodological variables (Thirion et al. 2007; Button et al. 2013; Clayson and Miller 2017; McGonigle 2012; Fehr et al. 2014) that should either be controlled or used as covariates for the explanation of respective statistical effects.

We note, however, that distribution characteristics of the source strength values and the respective regional II-estimates may not fulfill criteria for parametric testing. In this case non-parametric alternatives should be used (e.g.,

Mann–Whitney-U-Test for inter-regional and repeated measurement testing and Wilcoxon-Test for independent factors such as groups). Moreover, to account for interdependencies between voxels and the extensive number of tests required for voxel-wise testing, multiple testing corrections such as the non-parametric permutation test of the maximum statistic should be applied (e.g., Nichols and Holmes 2001).

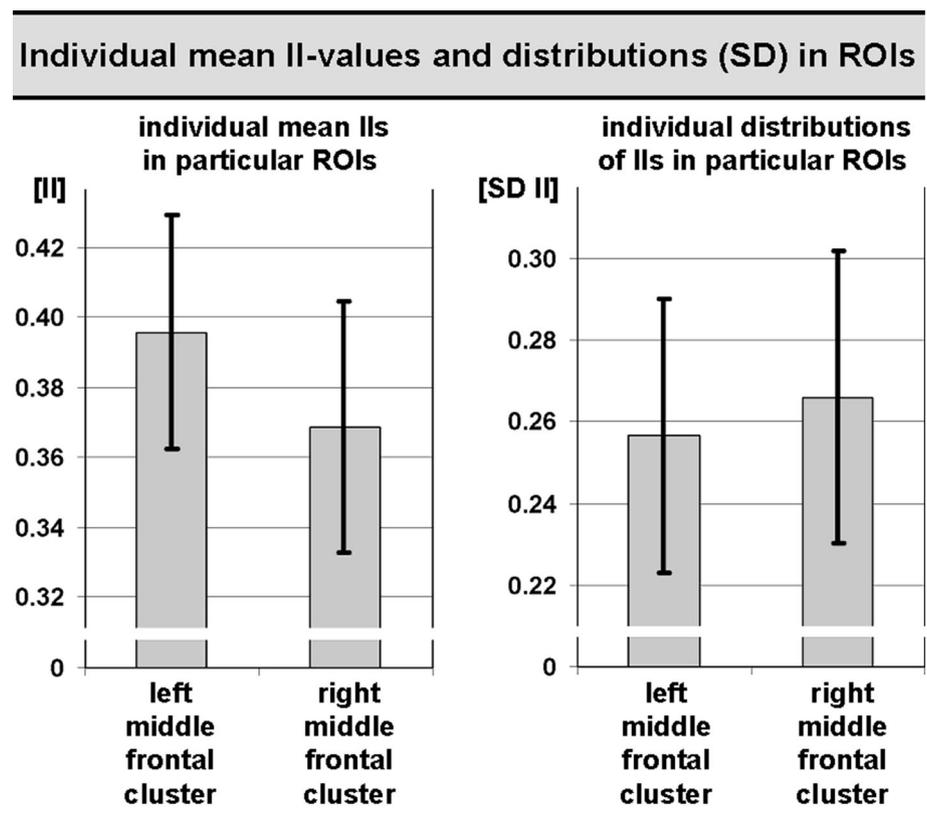
In sum, the proposed data analysis strategy can be regarded as a non-parametric step towards the identification of individual characteristics of spatio-temporal brain activation. It has the potential to shed light on the causes and associations of the largely neglected inter- and intra-individual differences so prominent in the neuroimaging literature. In particular, it can be used to explore different

Table 2 Mean (M) regional IIs and respective standard deviations (SD) for nine simulated individuals (in percentage-values); Overall mean for individual, regional means and respective standard deviations; further details and statistics see Sect. 3.2

IIs calculated on simulated data					
Data set	Mean ROI-IIs		Variations in ROI-IIs		
	M II LH	M II RH	SD II LH	SD II RH	
P01	0.38	0.36	0.25	0.26	
P02	0.40	0.35	0.26	0.25	
P03	0.40	0.37	0.26	0.27	
P04	0.38	0.41	0.25	0.30	
P05	0.39	0.40	0.26	0.29	
P06	0.35	0.36	0.22	0.26	
P07	0.47	0.31	0.30	0.22	
P08	0.38	0.34	0.25	0.25	
P09	0.41	0.42	0.27	0.30	
M of IIs	0.40	0.37	M of sx	0.26	0.27
SD of IIs	0.03	0.04	SD of sx	0.02	0.03

Means over individual IIs and respective SDs were illustrated in Fig. 3

Fig. 3 (Left panel) Bar charts illustrating mean regional IIs for nine simulated, individual data sets with respective standard deviations (error bars represent SDs) (see Table 2, left part for the corresponding values). (Right panel) Bar charts illustrating means over individual variations of IIs in the particular ROIs and the respective SDs (see Table 2, right part for the corresponding values). Paired t-tests did not reveal any significant differences between brain region means in the presented simulated data set (see Sect. 3.2 for details)



model assumptions about how (e.g., linear, curve-linear, logarithmic, deterministic) and to what spatial extent particular brain regions are involved during the execution of particular mental strategies, combinations thereof, and changes between them (cmp, Houdé and Tsourio-Mazoyer 2003, Fehr et al. 2011; Poldrack 2006; Fehr 2013).

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