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Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity

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Intra-individual variability reflects a transient, within-person change in behavioral performance. It is a common component of aging-related cognitive decline and the behavioral changes associated with neurodegenerative and other brain-related disorders such as traumatic brain injury and schizophrenia. Behavioral changes within an individual can reflect alterations at a systems or a cellular level in the brain, and monitoring intra-individual variability can therefore provide a warning of underlying pathology. Despite frequent reports of intra-individual variability, there is little synthesis, and no direct examination of the neural underpinnings. Here, we integrate seminal findings from cognitive research across lifespans of individuals, and also neuropsychological and neurobiological findings, to identify key questions and some potential answers, and to set challenges for fostering future research into intra-individual variability.

Intra-individual variability: concepts and implications

Most cognitive and neuropsychological research has focused on mean differences between groups such as slower responding for older than for younger adults, lower attentional capacity for schizophrenics than for controls, or poorer memory for persons with dementia relative to similarly-aged controls. This has largely overshadowed research on intra-individual variability, including trial-by-trial fluctuations in a reaction-time task or day-to-day variations of memory performance for a clinical sample. We argue that this is a serious theoretical and practical oversight. When intra-individual variability in performance is small, mean-level differences provide useful predictive information, but as intra-individual variability increases and represents systematic as opposed to random error, calculating mean performance from a single measurement occasion can lead to flawed estimates of average group differences [1]. Thus, an exclusive emphasis on mean levels without considering intra-individual variability is a crucial oversimplification of patterns of behavior and might lead to erroneous inference [2]. Indicators of intra-individual variability confer unique predictive information about cognitive functioning over and above mean performance [1,3], and have been found to render differences between populations more apparent [4,5].

Three primary indices of variability can be defined according to the number of persons, measures and occasions [6,7]. Between persons, variability reflects inter-individual differences in performance measured in a single task on a single occasion. Within persons, intra-individual variability has been defined in two ways: as the profile of performance across multiple tasks at a single point in time, and as fluctuations in performance of a single measure across trials within a task or across sessions spanning longer intervals (e.g. hours, days or weeks). The latter index reflects transient changes in behavior that can be distinguished from more enduring change (e.g. learning and development). Here, we chiefly focus on within-task intra-individual variability across closely spaced occasions (i.e. trials). With few exceptions, in the studies of intra-individual variability reviewed in this article, mean-level differences have been controlled. Thus, conclusions regarding group differences in intra-individual variability are not confounded by group differences in means.

Increased intra-individual variability characterizes performance of the elderly, and that of patients with dementia, head injury, attention-deficit hyperactivity disorder (ADHD) and schizophrenia. As early as 1926, Henry Head noted that 'an inconsistent response is one of the most striking consequences of lesions to the cerebral cortex' [8]. A possible link between intra-individual variability and the brain is suggested from both behavioral [1] and cognitive neuroscience [9] perspectives, but there has been little integration of the two fields. Therefore, we summarize and integrate research from psychology, neuropsychology and neuroscience on intra-individual variability across the lifespan, proposing approaches for analyzing brain correlates of intra-individual variability and identifying outstanding questions for future research.

Intra-individual variability across the lifespan

A U-shaped function characterizes the relationship between intra-individual variability in cognitive performance and age across the lifespan (Figure 1). Whereas

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intra-individual variability in performance decreases through childhood and adolescence [10,11], advancing age in later adulthood is associated with increasing intra-individual variability and concomitant impairment in performance [7,12]. This developmental pattern parallels the inverted U-shaped function observed for age-related changes in cognitive functioning [11], with maturation and senescence imposing age-specific constraints, particularly when the executive task load is high [13,14].

In the elderly, studies reveal pronounced age-related increases in intra-individual variability and concomitant impairments in attention, memory and language [7,12,15,16]. A striking observation is that intra-individual variability in perceptual-motor tasks over short intervals could correspond to as much as several decades of mean-level age differences in the same tasks [15]. Over longer intervals spanning as many as six years, increases in intra-individual variability have been associated with cognitive decline [17]. Intra-individual variability in cognitive functioning has also been linked to biomarkers of age, including forced expiratory volume, grip strength and visual acuity [18–20]. Further, over and above mean level, greater intra-individual variability predicts risk of mortality from all causes [21]. These observations suggest that intra-individual variability is a behavioral indicator of CNS integrity [1,9]. More specifically, increased intra-individual variability has been linked to frontal-cortex-mediated processes such as attentional lapses [22] and fluctuations in executive control [23]. Further evidence for this link comes from research showing that age-related increases in intra-individual variability are greater in task conditions that place greater demands on frontal-cortex-mediated executive processes [23].

Intra-individual variability and brain disorders

Impaired and more variable cognitive functioning has also been linked to neurodegenerative pathology and various other brain disorders. Converging evidence, from multiple sources and for diverse outcomes, indicates that increasing intra-individual variability is influenced by the CNS in general, and by the frontal lobes in particular.

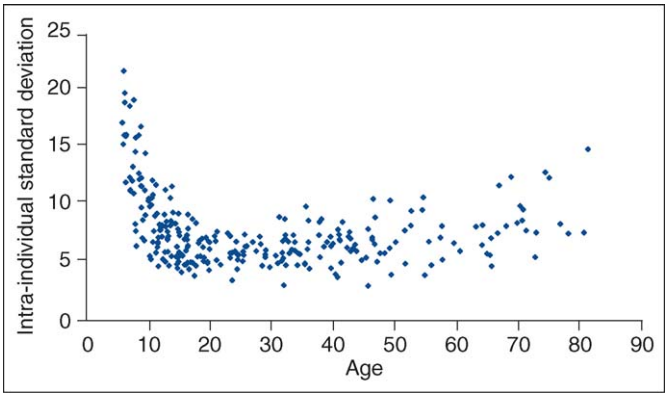

Figure 1. Intra-individual variability across the lifespan. Choice reaction time (CRT) was assessed across 32 trials for 273 participants aged 6–81 years. Potential confounds including practice effects across trials, age-related differences in mean performance level, and their interaction were first removed from the raw CRT data using a regression procedure. The residual scores from this regression were linearly transformed as t-scores with a mean of 50 and standard deviation of 10 across all data points. Intra-individual standard deviations were subsequently computed across the 32 CRT trials. The relationship between age and inconsistency across the lifespan was characterized by a U-shaped function, with advancing age throughout childhood, adolescence, and young adulthood associated with decreasing variability. By contrast, increasing age throughout older adulthood was linked to increasing variability. Reproduced, with permission, from Ref. [10].

Dementia

Mildly demented patients exhibit both increased intra-individual variability and cognitive impairment relative to similarly-aged healthy controls [4]. Importantly, increased intra-individual variability cannot be accounted for by non-neurological somatic conditions such as arthritis that influence motor control. The unique prediction of neurological status (demented versus healthy or arthritic) independent of mean-level performance is consistent with claims that intra-individual variability is a behavioral indicator of compromised neural mechanisms (Figure 2a). Recent research has also demonstrated increased intra-individual variability in reaction times for persons classified with mild cognitive impairment without meeting diagnostic criteria for dementia [24]. Finally, the magnitude of intra-individual variability differs across dementia subtypes. Individuals with frontal-lobe dementia exhibit increased variability in Stroop tests relative to Alzheimer's disease patients [5] (Figure 2b), reinforcing the point that the frontal lobes are crucial in mediating intra-individual variability.

Traumatic brain injury

Traumatic brain injury is associated with slower and more variable responding [25,26]. Patients with focal frontal lesions exhibit greater intra-individual variability in reaction times than controls and patients with non-frontal lesions [27]. These patterns, as a function of head injury and injury location, parallel differences observed for the dementias [5]. Further emphasizing the central importance of the frontal lobes, failures in memory for the sources of information are associated with higher intra-individual variability [28]. This relates to the well-known observation that source memory draws on the integrity of frontal-lobe functioning [28,29].

Attention deficit hyperactivity disorder

In early life, it has been noted that increased intra-individual variability is one of the most striking clinical characteristics in ADHD [30]. More variable responses in reaction-time tasks differentiate between children with and without ADHD [31], and deficits in temporal processing are proposed to account for the observed differences [30]. Consistent with increased intra-individual variability, reaction-time distributions for ADHD children are characterized by increased spread in addition to larger tails [32]. Findings from twin studies indicate a genetic link between hyperactivity and intra-individual variability [33,34]. This point was recently extended in research showing that adolescents carrying two copies of a high-risk allele for ADHD (a ten-repeat allele of the dopamine transporter gene) displayed increased intra-individual variability in an attention task [35].

What does increased intra-individual variability reflect?

Established links between intra-individual variability in behavior and the brain are sparse, with most evidence

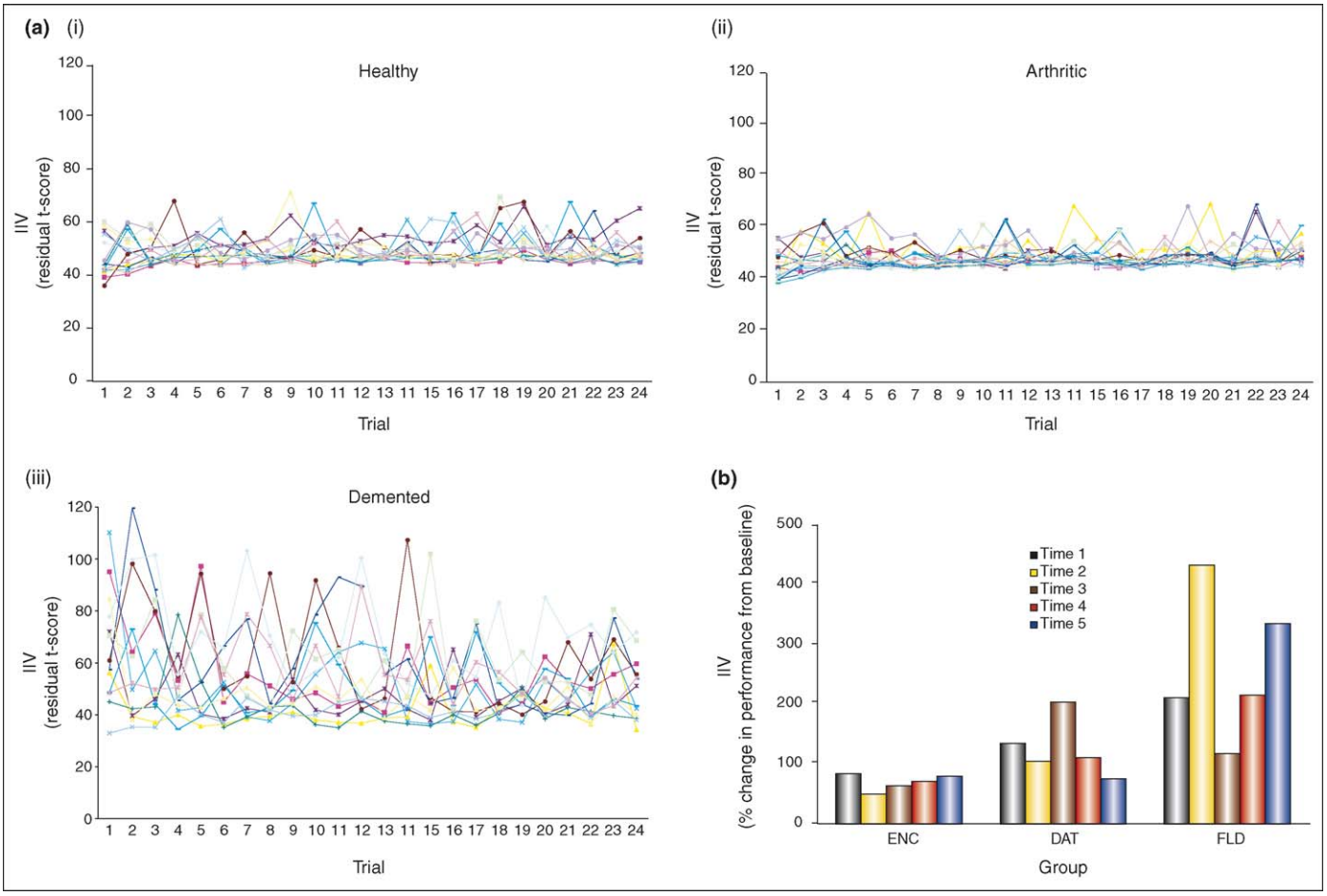

Figure 2. Group differences in intra-individual variability as a function of neural integrity. **(a)** Response latency across 24 episodic word-recognition trials in controls (i) and in persons with arthritis (ii) or mild dementia (iii). Residual t-scores of latency data for correct recognition trials, controlling for systematic group, practice and interaction effects, are plotted across trials as a function of group. Although group differences in mean level performance and change were statistically partialed ($M = 50$ for groups averaged over occasions, occasions averaged over groups, and each group by occasion cell), there are sizeable group differences in intra-individual variability (IIV). Participants with mild dementia showed, on average, approximately twice as much intra-individual variability in performance as neurologically-intact participants. Patterns of intra-individual variability did not differ between the healthy control group and an otherwise healthy group with arthritis, implicating endogenous neurological dysfunction rather than somatic disturbances as the source of increased variability. Reproduced, with permission, from Ref. [4]. **(b)** Two matched groups of subjects with dementia – dementia of the Alzheimer type (DAT) and frontal-lobe dementia (FLD) – and elderly normal controls (ENC) were compared to examine whether increased variability differentially reflects frontal-lobe pathology. Three Stroop subtests were administered weekly for five weeks in the same order of increasing difficulty. In these tests, subjects were asked to name the colors of 24 colored dots, of 24 colored words, and of 24 colored color words where the ink color was incongruent with the verbal referent (e.g. 'blue' displayed in green ink). Performance fluctuations across time were indexed as the difference between the colored-color-word and dot conditions (a measure of interference sensitive to frontal-lobe function) divided by the response time required to name the colored dots. This measure of variability controlled for initial group differences in baseline dot performance time. Whereas the FLD group exhibited higher variability than the other two groups, the ENC and DAT groups did not differ. The greater intra-individual variability over time for the FLD group supports the hypothesis that frontal-lobe dysfunction subserves increases in intra-individual variability. Reproduced, with permission, from Ref. [5].

being indirect. Based on current evidence, increases in behavioral intra-individual variability seem to reflect multiple neural determinants. In this section, we synthesize available research to identify plausible neural correlates of intra-individual variability, speculate on potential mechanisms, and outline future possibilities for measuring intra-individual variability in the brain.

Structural correlates of intra-individual variability

Lesions to frontal gray matter [27] and white matter alterations [36] have been suggested to underlie intra-individual variability. In addition, the nonlinear developmental changes in behavioral intra-individual variability and documented nonlinear structural changes at both ends of life relate intra-individual variability to brain structure. Thus, previously reported behavioral decreases in intra-individual variability from childhood through adolescence [10] might reflect systematic changes in brain morphology, particularly in the frontal lobes [37]. Among possible mechanisms, reductions in gray-matter density coincide temporally with synaptic pruning during adolescence and young adulthood [37,38]. Such reductions could increase neural efficiency and decrease noise in cognitive functioning, and might underlie concomitant decreases in intra-individual variability during development [37]. Similar arguments apply to reductions of gray matter in the elderly [38,39]. White matter volume also shows marked changes across the lifespan, approximating an inverted U-shaped function similar to that for behavioral intra-individual variability [10,40] (Figure 1). In sum, the neural system matures, levels off, and then begins to decline, with a direct mapping of increasing then decreasing intellectual functioning [11] to decreasing then increasing behavioral intra-individual variability [10].

Neuromodulatory correlates of intra-individual variability

Dysfunctional modulation of select neurotransmitters, including those in the catecholamine and ACh systems, gives rise to increased neural noise [41,42] that might contribute to increased intra-individual variability in cognitive performance. In particular, alterations in the dopamine system are documented in select populations [30,41] that also exhibit increased behavioral intra-individual variability, including the elderly [7,12], ADHD children [30,35], schizophrenics [43] and patients with Parkinson's disease [44]. These findings have been substantiated in computational modeling studies showing that reduced dopamine activity increases neural noise, resulting in less distinct cortical representations manifest as decreases in cognitive performance and increases in behavioral intra-individual variability [45–47].

The catechol *O*-methyltransferase (COMT) enzyme degrades dopamine in the frontal cortex [48]. Carriers of the Val allele of the *COMT* gene have lower dopamine levels in the synaptic cleft than Met carriers because of higher enzymatic activity. It was recently demonstrated that Val carriers were more variable than Met carriers in a rapid perceptual comparison task, thereby linking dopamine activity to intra-individual variability [46,49]. Although these findings implicate dopaminergic neurotransmission in intra-individual variability, further research is required to more precisely delineate the underlying mechanisms (Box 1).

Functional brain imaging correlates of intra-individual variability

Whole-brain functional activation techniques, such as electroencephalograms (EEGs) and functional magnetic resonance imaging (fMRI), can potentially link behavioral intra-individual variability to brain function. Select investigations have examined event-related oscillations in the EEG band in relation to cognitive performance. Psychometric intelligence shares an inverse relationship with event-related potential variability in the parietal and temporal lobes [50], and increased variability in P300 latencies, an electrophysiological marker of cognitive processing, has been linked to old age and morbidity [51]. Increases in prefrontal EEG responses during information processing are negatively correlated with working memory performance in schizophrenics, their siblings and healthy controls, and might be a function of asynchronous field potential oscillation by cortical pyramidal neurons [52,53] (Figure 3a).

The EEG data showing increased prefrontal broadband noise in schizophrenics were related to increased fMRI activation in the dorsolateral prefrontal cortex (DLPFC) during a working memory task, a pattern interpreted to reflect inefficient neural processing [53] (Figure 3b). It is interesting that similar increases in DLPFC activity during working memory performance have been documented in carriers of the Val allele of *COMT* [49,54] (Figure 3c). Further, a recent review of neuroscientific perspectives of aging summarized the importance of intra-individual

Box 1. Connecting behavioral intra-individual variability to brain functions

Experimental manipulations

Manipulating select brain correlates associated with variability represents one approach to link behavioral intra-individual variability directly to brain function. For example, by enhancing or hampering the activity of the dopamine system through the provision of agonists or antagonists, direct effects of dopamine signaling on behavioral intra-individual variability could be examined. Dopamine agonists influence multi-second oscillations in the basal ganglia firing rate that coordinate neuronal activity underlying motor sequences, movement timing and attentional processes [64]. Given the known importance of dopamine to age-related cognitive impairment [41] and the hypothesized importance of dopamine to intra-individual variability, administration of a dopamine agonist might decrease intra-individual variability in reaction time for the elderly, whereas a dopamine antagonist might increase intra-individual variability in reaction time for the young. Although agonist and antagonist manipulations have known effects on mean-level cognitive performance [41,42], it remains unknown whether such manipulations would influence intra-individual variability.

Single-cell recordings

Examining across-trial variability in firing rate for single cells represents another direct approach. Single-cell recordings from the frontal eye field of rhesus monkeys indicate that eye movements are triggered only after neural activity has surpassed a specific and constant threshold of activation, with variability in the timing of voluntary movements due to stochastic variability in the growth rate of the neural activation function [65]. *In vivo* recordings of neocortical neurons in cats reveal reverberating (synchronous) temporal patterns of activation such that the firing sequence of spikes reoccur over tenths of seconds; this recurring pattern can be blocked by a dopamine antagonist [66]. In humans, the relative timing of the first spikes contains reliable information about, for example, object shape [67]. Although these data link neuronal timing information to behavior, it remains to be determined whether cellular synchronization patterns map onto behavioral intra-individual variability.

High-field fMRI

Recent technological advances in event-related fMRI (e.g. high-field 4T MRI) have enabled the rapid measurement of changes across BOLD signal trials [58]. That is, rather than computing within-person estimates across BOLD trials and then averaging across subjects, it is possible to analyze data across BOLD trials within subjects.

Adopting this approach, intra-individual variability in brain functioning can be examined by computing a within-person variability index across activation trials (intra-individual variability in percentage signal change), with the distribution of the BOLD response itself reflecting the outcome of interest (Figure I). If behavioral intra-individual variability is a proxy for neural processes, then indices of brain intra-individual variability should be systematically associated with intra-individual variability in cognitive performance. Thus, within-person coupling can be tested stringently by computing the time-varying covariation of intra-individual variability for discrete blocks of reaction-time trials in relation to intra-individual variability of BOLD responses for the corresponding trials.

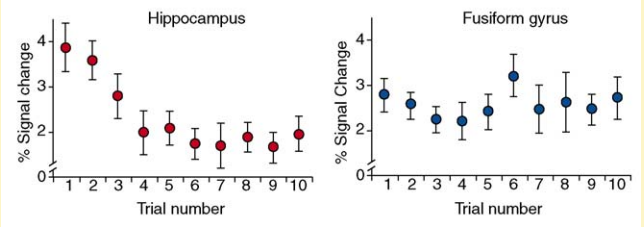

Figure I. BOLD signal changes within single trials for novel stimuli from a high-field 4T MRI. Effects of stimulus repetition on BOLD signals in response to novel stimuli in the hippocampus and the fusiform gyrus. In the hippocampus, a pronounced novelty effect was observed with maximal activity at trial 1 and markedly lower activity by trial 4. Activity in the fusiform gyrus was insensitive to the relative novelty of stimuli. Adapted, with permission, from Ref. [58].

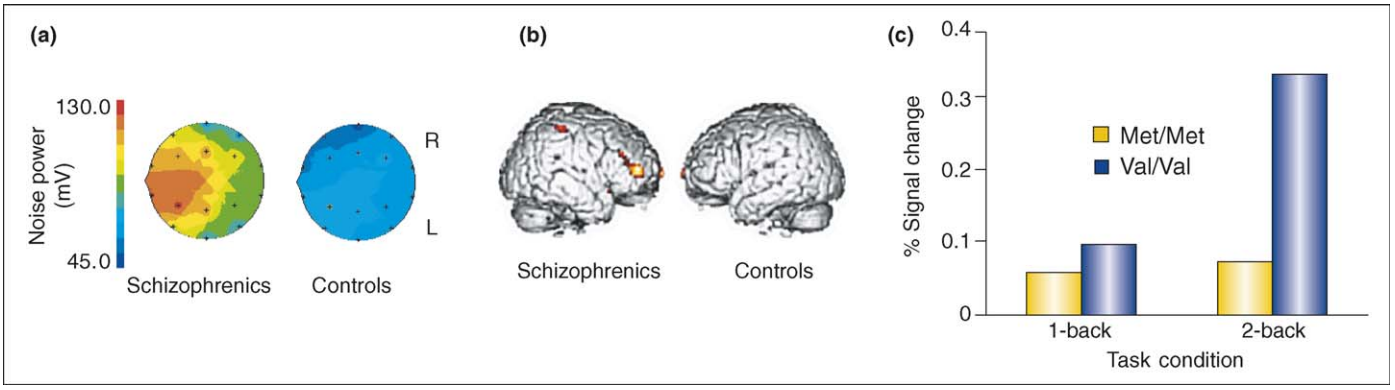

Figure 3. Linking behavioral intra-individual variability to brain function. **(a)** Mean topographic maps of event-related EEG during an auditory oddball task, showing increased 'prefrontal noise' in schizophrenic patients compared with normal controls in the theta-frequency band (6.0–8.0 Hz). Response variability or noise (i.e. activity not time-locked to the stimuli) was approximated by subtracting the mean magnitude of the single trials from the magnitude of the average potential, with schizophrenics exhibiting a relatively unstable prefrontal response. These results suggest that schizophrenia involves variable processing in prefrontal cortical microcircuits. This EEG noise index was inversely correlated with working memory performance in both groups, suggesting that it reflects a functional state of microcircuits subserving cognitive processing in the prefrontal cortex. 'R' and 'L' indicate right and left sides of the brain, respectively. Adapted, with permission, from Ref. [45]. **(b)** fMRI activation maps for a 2-back working-memory task, requiring the subject to recall the stimulus presented '2' stimuli previously, show prefrontal areas in which schizophrenic patients are inefficient compared with normal controls when task performance does not differ between groups. In fMRI research, 'inefficiency' denotes excessive activity for a given level of performance and is assumed to reflect unfocused or unstable response circuits [53]. Adapted, with permission, from Ref. [52]. **(c)** Percentage change in BOLD signal in the left prefrontal cortex during *n*-back relative to control tasks as a function of *COMT* genotype. For a fixed level of *n*-back performance, subjects homozygous for the Val allele (who have lower dopamine activity) demonstrated greater prefrontal cortex activity than homozygous Met carriers (who have higher dopamine activity). This difference increased as a function of executive task load (i.e. 2-back versus 1-back condition). The greater prefrontal cortex response in Val carriers indicates a less efficient physiological response, probably reflecting reduced prefrontal neuronal signal-to-noise ratio. Adapted, with permission, from Ref. [54].

variability as a marker of age-related cognitive impairment [9], with older adults non-selectively recruiting task-irrelevant brain regions during episodic and working memory performance [55,56]. Thus, a less efficient frontal response during cognitive processing characterizes schizophrenics, COMT Val carriers and the elderly – all groups displaying increased behavioral intra-individual variability and alterations in the dopamine system.

Although this association between diffuse neural activation and intra-individual variability is suggestive, it is based on comparisons between experiments. Within-experiment evidence was provided in an fMRI study in which a measure of intra-individual variability was related to neural activity during a response inhibition task [57]. Increased intra-individual variability was associated with increased brain activity in left and right middle frontal regions (Figure 4), which was related to a greater demand for executive control to maintain task performance. However, although promising, these patterns do not reflect across-trial variability in the brain. A more direct approach requires examination of fluctuations in the blood-oxygen-level dependent (BOLD) signal for individual trials across subjects. High-field MRI scanners can resolve rapid changes in the signal [58], permitting computation of a BOLD intra-individual variability index over consecutive trials (Box 1).

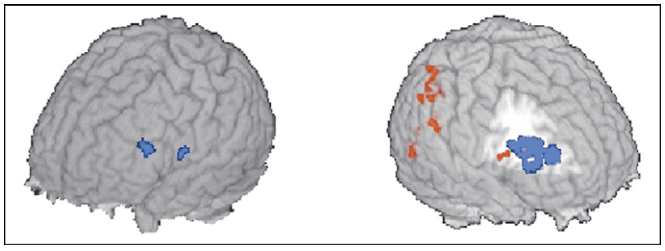

Figure 4. Functional neuroanatomical correlates of intra-individual variability. Increased behavioral intra-individual variability for a response-inhibition task (Go–NoGo) was associated with lower inhibitory success and slower responding. Controlling for individual differences in mean response times, increased behavioral intra-individual variability was associated with increased brain activity in middle frontal and left precentral areas (blue regions on the left) and right middle frontal regions (blue regions on the right). Persons with higher intra-individual variability activate inhibitory regions to a larger extent, probably reflecting greater requirement for top-down executive control. Red denotes regions that are beyond the scope of this review. Adapted, with permission, from Ref. [57].

Noise: a caveat

Although our focus has been on the negative aspects of variability, positive implications should also be considered [59]. In physical and biological systems, the presence of noise putatively degrades information processing. However, research on stochastic resonance shows that random noise enhances detection of weak signals, thereby facilitating information processing in the brain [60]. For example, applying subsensory mechanical noise to the feet of elderly adults improves motor control and reduces postural sway to nearly the level of young adults [61]. Future research should continue to examine potential sources of neural noise and further consider the potential of stochastic resonance to improve signal processing [62].

Concluding remarks

We have synthesized evidence on the neural underpinnings of behavioral variability. The available data suggest that variability can have multiple origins. Changes in gray-matter density, whether caused by development, lesions or neurodegeneration, are likely to affect variability. Disconnectivity in associative pathways, caused by immature or degraded white matter tracts, can also increase variability. In addition, variability has neuromodulatory correlates, with many populations characterized by increased performance fluctuations also exhibiting altered dopamine functions. Spanning these neural origins, increased variability is most strongly linked to frontal brain regions. This point is substantiated by the findings that more variable persons show less efficient frontal responses during cognitive

processing [57], and that variability increases in frontal-cortex-mediated executively demanding tasks [23]. The biological underpinnings of variability are not mutually exclusive, but clearly interact. For example, increased variability due to faulty dopamine-mediated neurotransmission could have a bottom-up origin as in Parkinson's disease, but could also be due to deficient top-down regulation by prefrontal regions following lesions or in schizophrenia [63].

Future research should provide more mechanistic evidence on the brain–variability relationship. This could involve pharmacological manipulations of potential neural substrates of variability such as dopamine. Further, it is vital to link variability in brain and behavior directly. Here, studies of the temporal dynamics of single neurons and neuronal ensembles, and of the fMRI BOLD signal, constitute promising avenues.

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