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Neural variability: friend or foe?

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Although we may not realize it, our brain function varies markedly from moment to moment such that our brain responses exhibit substantial variability across trials even in response to a simple repeating stimulus. Should we care about such within-subject variability? Are there developmental, cognitive, and clinical consequences to having a brain that is more or less variable/noisy? Although neural variability seems to be beneficial for learning, excessive levels of neural variability are apparent in individuals with different clinical disorders. We propose that measuring distinct types of neural variability in autism and other disorders is likely to reveal crucial insights regarding their neuropathology. We further discuss the importance of studying neural variability more generally across development and aging in humans.

Sources of neural variability

Moment-to-moment neural variability is generated by many neurophysiological mechanisms. At the single cell level, these include the noisy response characteristics of peripheral sensors [1], the stochastic nature of synaptic transmission [2], and the dynamic changes caused by neural adaptation [3] and synaptic plasticity [4]. At the neural network level, additional variability is generated by adjustments of the excitation/inhibition balance [5], changes in attention and arousal levels [6], continuous interaction and competition across large neural populations [7], and distributed neuromodulation effects [8]. Working together, these mechanisms (and others) generate substantial variability such that neural responses to even a simple, mundane stimulus differ markedly across trials of an experiment [9–13].

Estimating the amount of neural variability associated with each of the sources described above in humans is difficult. However, when measuring within-subject neural variability using neuroimaging and electrophysiology techniques, it is possible to decompose neural variability into variability that appears in early versus late parts of the stimulus/task evoked response, variability that is specific to a local brain area versus variability that is shared across the entire brain, and ongoing neural variability that appears in resting-state recordings where the stimulus or task are absent (Box 1). Do these distinct measures of neural variability tell us anything about the integrity of the individual's brain function? Are particular levels of neural variability indicative of the individual's perceptual and cognitive abilities or their clinical state?

Excessive neural variability in autism

Autism is a developmental disorder which is diagnosed based on the presence of specific behavioral symptoms that include social communication difficulties, abnormal sensory sensitivities, and repetitive behaviors [14]. Prominent hypotheses about autism posit that it may result from excitation–inhibition imbalances [15–17], abnormalities in genes that govern neural migration and proliferation [18,19], and synaptic maturation and transmission [20,21]. Such fundamental neural alterations are hypothesized to create widespread neural processing abnormalities [22,23], which may include excessive neural variability/noise [16,24,25].

In support of this hypothesis, several fMRI [26–28] and electroencephalography (EEG) [29,30] studies have reported that brain responses of high-functioning individuals with autism exhibit excessive trial-to-trial variability in comparison to brain responses of matched controls. In two of these studies, we examined the trial-to-trial variability of fMRI response amplitudes when participants were presented with simple visual, auditory, or tactile stimuli in three independent experiments. Although the mean fMRI response amplitudes across trials in each sensory domain were indistinguishable across the two groups, the standard deviation across trials was approximately 20% larger in the autism group in all three sensory systems (Figure 1). These findings suggest that excessive neural variability is a widespread phenomenon apparent in the responses of multiple sensory systems (and potentially other brain systems as well) in autism.

Although excessive neural variability was apparent in these sensory-evoked responses, it was not present in comparisons of ongoing ('resting state') neural fluctuations [26,27], suggesting that increased neural variability in autism was specifically associated with sensory evoked processes rather than with ongoing neural fluctuations. Note that, by dissociating neural variability in these two distinct situations (resting state and stimulus-evoked), it is possible to separate the contribution of different underlying physiological mechanisms that drive neural variability (Box 1). Additional analyses revealed that the level of neural variability within each participant was consistent across the different sensory experiments (Figure 2), suggesting that neural variability was a stable characteristic of each participant's brain, and this was similarly evident across all examined sensory systems.

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Box 1. Measuring multiple components of neural variability in humans

Neural variability can be separated into several distinct and measurable components. When recording brain activity using EEG, it is possible to separate variability at different latencies from stimulus or task onset. For example, when performing an event related potential (ERP) analysis, it is possible to identify commonly described early and late peaks of the ERP, such as the N1 and P2 of an auditory evoked response, which are thought to represent different underlying sensory and cognitive processes [91], and assess the trial-to-trial variability of each (see Figure 3A in main text). When recording brain activity with fMRI, it is possible to separate variability across space. For example, it is possible to separate 'local' variability from 'global' variability by measuring trial-by-trial variability in a local region of interest before and after regressing out the global mean grey matter time-course (see Figure 3B in main text). Finally, variability associated with ongoing (i.e., resting state) activity can be separated from variability associated with stimulus-evoked or task-evoked activity by computing trial-to-trial variability before and after stimulus/task onset, by assessing variability on trials where the stimulus was absent (see Figure 3A in main text), or by examining longer resting-state recordings during which no stimulus is presented and no task is performed. Such comparisons have been carried out extensively in electrophysiology studies with animals [13,92], but have rarely been performed in human EEG and fMRI studies.

When estimating neural variability in humans using neuroimaging techniques, it is important to remember that each technique is prone to large sources of measurement noise. For example, fMRI scans are susceptible to head-movement artifacts [93], and EEG measures are susceptible to saccade and eye-blink artifacts [94]. It is, therefore, particularly important to measure and control external (non-neural) sources of variability when attempting to characterize trial-to-trial neural variability.

How might excessive neural variability be associated with the core social, sensory, and repetitive behavior symptoms that define autism? We speculate that variable, unreliable neural responses in multiple sensory and associative brain areas during early autism development may create an unstable and unpredictable perception of the environment. Increased neural noise may be associated with more neural plasticity, as demonstrated in some animal models of autism [16] (also see section below about development). In such a situation, individuals with autism may indeed find it difficult to learn the correct probabilities and statistics of external events and, therefore, exhibit difficulties in predicting their environment [31–34]. This unpredictability may be particularly accentuated in social situations where humans (unlike objects) display a wide variety of variable social and emotional cues, which must be perceived using multiple sensory modalities [35]. Developing under such conditions may motivate an infant to retract from social interactions and engage in repetitive behaviors (often involving objects) that are likely to generate more predictable neural responses. In addition, excessive neural variability in sensory and motor systems may explain why individuals with autism exhibit balance problems, motor clumsiness [36], differences in visual perception [24,25] (see section below about perception in autism), and abnormally large behavioral variability in trial-to-trial reaction times [37,38], eye saccade accuracy [39], reaching movement accuracy [40], and pitch of voice during speech [41]. Previous studies have also suggested that unstable/noisy neural networks are more likely to develop epileptic seizures [15], which are indeed more prevalent in autism than in the general population [42].

Although excessive neural variability has so far been reported only in sensory and motor systems of individuals with autism, these findings may indicate a more fundamental and widespread physiological alteration in autism that might perturb neural processing across many brain systems. Recent theoretical discussion on this topic has proposed that both reduced and increased endogenous neural noise at the level of the single neuron or small-scale, local neural circuits may generate the increase in large-scale trial-to-trial variability demonstrated by the EEG and fMRI studies mentioned above [43,44]. Systematic characterization of neural variability at different levels of sensory, emotional, and social processing, and at different stages of development (with a particular focus on early development), is highly warranted for assessing these ideas.

Another influential hypothesis is that autism is caused by abnormalities in synchronization of neural activity across distant brain areas as assessed with functional connectivity techniques that measure the correlation in activity across brain areas [45,46]. Numerous neuroimaging studies have indeed reported that toddlers [47], children [48], adolescents [49], and adults [50,51] with autism exhibit abnormal functional connectivity in contrast to matched controls. In addition, studies using diffusion tensor imaging (DTI) techniques have revealed that children,

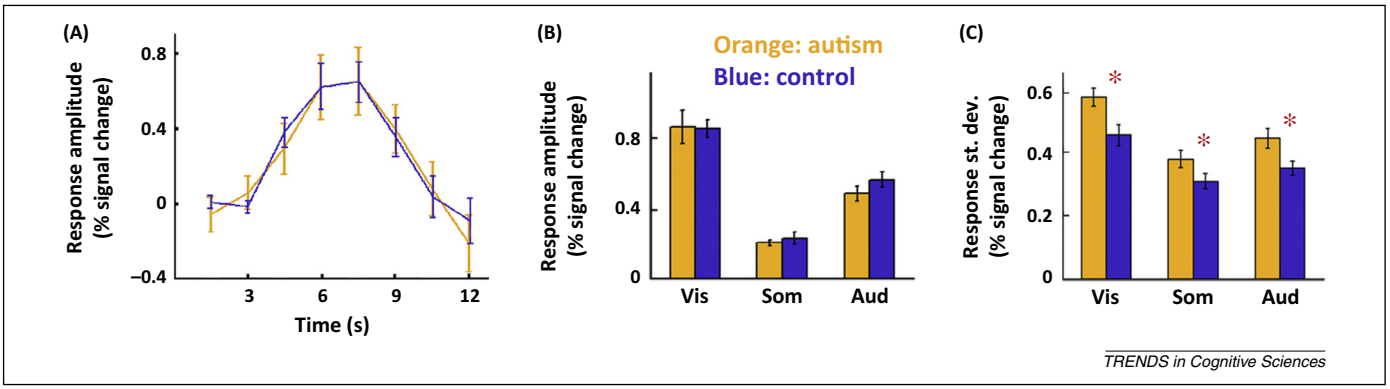

Figure 1. Excessive neural variability in adults with autism demonstrated across the visual (Vis), auditory (Aud), and somatosensory (Som) systems. **(A)** Mean hemodynamic response time-courses from a single subject with autism and a single control subject in an auditory experiment. Error bars, standard error across trials. **(B)** Mean response amplitudes, averaged across trials and across subjects in each group. **(C)** Standard deviations of response amplitudes across trials. Orange, autism; blue, control. Red asterisks, significant difference between groups ($P<0.05$, one-tailed t-test); error bars, standard error across subjects. Figure adapted from [26].

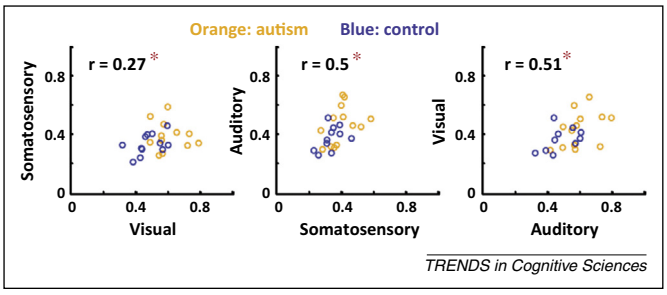

Figure 2. Consistency of within-subject standard deviation across trials in multiple sensory modalities. Each panel demonstrates the correlation between trial-to-trial standard deviation in a pair of sensory experiments [26]. Each point represents the standard deviation of a single subject. Correlation r values across all subjects (both groups) are presented in each panel. Orange, autism; blue, control. Red asterisk, significant correlation as assessed using a randomization analysis ($P<0.05$) in which the identity of subjects was shuffled randomly 10 000 times to create a null distribution of the correlation values expected by chance. To achieve statistical significance the real correlation values had to exceed the 97.5 percentile of the null distribution.

adolescents, and adults [52] (but not toddlers [53]) with autism exhibit smaller and less-developed white matter tracts in comparison to matched controls. Excessive neural variability may be related to these findings in two manners. First, the presence of local independent neural noise in each brain area would be expected to reduce functional connectivity across brain areas, because the independent noise in one brain area would be, by definition, uncorrelated with the noise of the other brain area (whether the noise apparent in distinct brain areas of individuals with autism is indeed independent or not remains to be determined). Second, because function and structure are intimately linked throughout development, reduced correlation in activity across brain areas during early development may result in abnormal anatomical connectivity, as demonstrated by DTI studies. The relationship between neural variability and functional or structural connectivity throughout development has not been examined thus far.

An additional hypothesis is that individuals with autism develop altered perceptual systems that exhibit heightened sensitivity to details [54] together with an impaired ability to integrate details coherently into gestalt percepts [55] such as faces [56]. Whereas a heightened sensitivity to details seems to be at odds with the idea of excessive neural variability, it has been proposed that the greater presence of neural noise in autism may have a counterintuitive beneficial effect of enhancing detection of details as a result of stochastic resonance [24]. Stochastic resonance describes a general phenomenon whereby adding random noise to an extremely weak signal elevates the chances of detecting the signal with a wide variety of detection systems, including biological sensory systems [57]. This may bias children with autism to focus on details rather than attempt to integrate them, thereby altering typical learning and memory strategies [24].

Finally, note that individuals with autism exhibit not only larger within-subject variability but also larger between-subject variability. This is apparent, for example, in both the variable topography of brain activations across individuals [58,59] and the idiosyncratic nature of cortical responses to movies [56].

Variability in other clinical disorders

Is excessive neural variability unique to autism? Several studies have reported that excessive neural variability is also apparent in other disorders, but suggest that different disorders exhibit distinct types of neural variability. For example, individuals with dyslexia exhibit abnormally large trial-to-trial variability in auditory brain stem EEG responses to single syllables [60]. By contrast, individuals with attention deficit hyperactivity disorder (ADHD) exhibit abnormally variable P3b (P300) responses, which are thought to represent late decision-making processes rather than early sensory processes [61]. Finally, a large fMRI study reported that patients with schizophrenia exhibit excessive variability in ongoing, resting-state activity, which was not apparent in either a matched control group or a group of obsessive-compulsive disorder (OCD) patients [62]. Taken together, it seems that individuals with autism, dyslexia, ADHD, and schizophrenia, but not OCD, exhibit distinct forms of excessive neural variability in comparison to control individuals. Additional direct comparisons across patient populations using identical experimental designs, analysis methods, and neuroimaging techniques will be highly valuable for determining which of the reported abnormalities are unique to each population and which are overlapping or shared.

What do these results tell us about the potential underlying pathophysiology of each disorder? When considering the different sources or mechanisms of neural variability, it is tempting to speculate that distinct measures of neural variability may be more strongly associated with some mechanisms than others. For example, excessive ongoing (i.e., resting state) neural variability may be caused by abnormally unstable neuromodulation. Additional distinctions across disorders may include the developmental timing of excessive variability (e.g., early childhood versus advanced aging), its severity, and spatial distribution (e.g., subcortical versus cortical, and sensory versus motor). Finally, it is entirely plausible that some types of excessive neural variability may appear across several disorders that may share pathophysiological mechanisms. Note that numerous genetic risk factors are shared across the disorders described above [63–65]. In such cases, assessment of neural variability may still be useful for developing measures of clinical severity and prognosis, as well as in designing potential novel treatments and testing their efficacy. There are many cases in which different disorders (e.g., depression and anxiety) present overlapping symptoms and benefit from identical therapies [e.g., the administration of selective serotonin reuptake inhibitors (SSRIs)], which apparently affect shared pathophysiology [66].

Cognition and perception

Might specific measures of neural variability indicate anything about an individual's cognitive or perceptual abilities? An extensive body of behavioral research has shown that larger trial-to-trial behavioral variability is apparent in individuals with different cognitive impairments [67]. These include reports of increased reaction time (RT) variability in individuals with dementia [68], traumatic brain injury [69], schizophrenia [70], autism [37,38],

and ADHD [71–73] across a wide range of working memory, sustained attention, and response inhibition tasks. Although behavioral variability lacks specificity to a particular disorder, it appears to be a potent measure for assessing clinical severity and the effects of treatments. For example, RT variability increases with the severity of ADHD [74] and decreases following the use of Ritalin [75]. The potential relationships between specific measures of neural variability and RT variability or different elements of cognitive performance have not been examined thus far, but it is tempting to speculate that trial-to-trial behavioral variability may be generated by underlying trial-to-trial neural variability.

Excessive neural variability may also have maladaptive effects on perception as suggested by studies that estimate internal (or equivalent) noise levels – a measure that represents the amount of neural noise inherent in the sensory system of an individual [76]. This measure is estimated behaviorally by characterizing the sensitivity thresholds of an individual to stimuli with and without the addition of external noise [77]. It has been reported that larger internal noise limits the ability of an individual to detect a signal, such that individuals with higher levels of internal noise have higher detection thresholds [78]. Individuals with different disorders including migraine [79] and dyslexia [80] exhibit larger levels of internal noise as measured with these techniques, but the potential relationships between such internal noise measures and different forms of neural variability have not been examined thus far.

Variability in motor learning and typical development

Although excessive neural and behavioral variability may be indicators of impaired cognitive function and pathophysiology, a degree of neural and behavioral variability is essential for learning and proper development. Variability is a central component of many motor control models that explain how the motor system balances the need for accuracy and the need for flexibility [81]. Performing accurate actions in an ever-changing world means that the motor system constantly needs to adapt to both internal (e.g., injured muscle) and external (e.g., slippery surface) perturbations. It is thought that even adult motor systems achieve better performance by actively generating variability that leaves room for adaptive plasticity/flexibility through continuous trial-and-error monitoring [82]. Behavioral variability increases during active motor learning [83], a process that is thought to depend on the active release of dopamine in cortico-striatal neural circuits [84]. This mechanism is thought to enable the individual to explore variable motor outcomes and then select and stabilize motor behavior that is associated with the highest

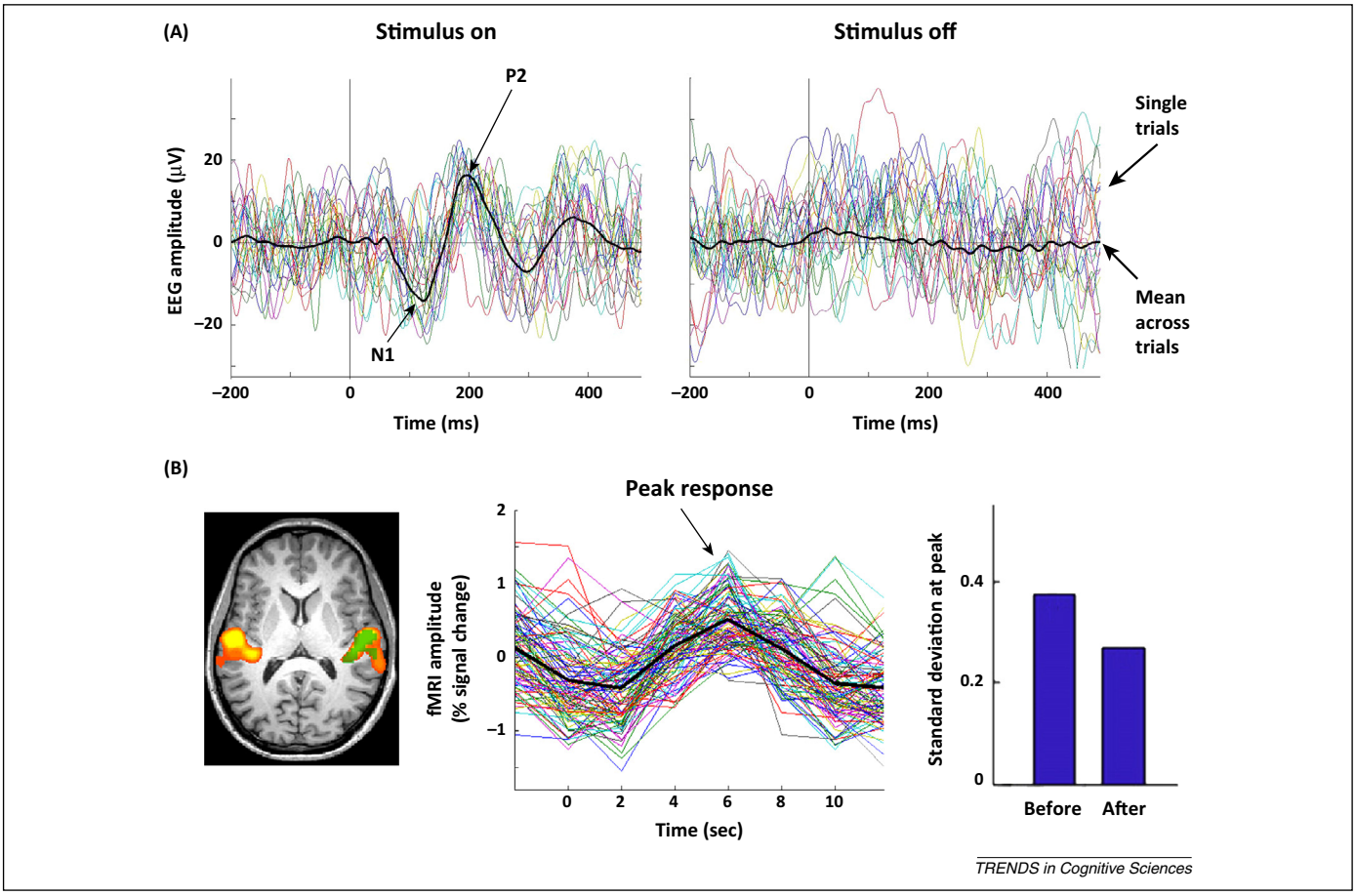

Figure 3. Measuring neural variability. **(A)** Auditory evoked responses to pure-tone beeps from a single subject during stimulus-on trials (left) and stimulus-off catch trials (right). Comparison of trial-to-trial variability in the two cases enables assessment of variability due to ongoing fluctuations (stimulus off) and stimulus-evoked responses (stimulus on) **(B)** fMRI evoked responses of a single subject to pure-tone beeps, extracted from a region of interest marked in green. Performing the analysis before and after regressing out the global mean (right panel) can reveal the extent of 'local' versus 'global' variability. Single trial responses are in color and the mean across trials is in black. Data collected from a neurotypical adult in the lab of I.D.

reward or accuracy [83]. In patients with Parkinson's disease, in which dopamine is depleted, the ability to learn new movements and adapt to perturbations is dramatically reduced [85].

Additional benefits of behavioral and neural variability are apparent in studies of early development. Young children [86] and immature songbirds [87] show large behavioral variability, which decreases with development. This suggests that behavioral and neural variability is a pivotal strategy for exploration and learning, and is characteristic of early developmental periods associated with high plasticity. Indeed, it has been reported that neural populations in the lateral magnocellular nucleus of the anterior nidopallium (LMAN) of juvenile songbirds actively generate behavioral (vocal) variability during song learning, which is essential for successful song maturation [87].

Elderly individuals, like children, also exhibit greater trial-to-trial behavioral variability than do younger adults across a wide range of cognitive tasks [88]. In the elderly, however, increased variability is associated with a decline in cognitive abilities such as sustained attention [89], response inhibition [90], and working memory [90]. Hence, whereas large variability during early development seems to be beneficial, and coincides with periods of enhanced learning and exploration, the same phenomenon in the elderly seems to indicate deteriorating brain function associated with impaired cognition.

Concluding remarks and future directions

The human brain seems to balance the need to perform tasks accurately and respond to stimuli reliably (on a single-trial basis) with the need to maintain flexibility, explore novel solutions and outcomes, and adapt to ever-changing environmental conditions. Neural variability is likely maladaptive for optimizing performance accuracy on single trials, but it seems to be important for enabling exploration, plasticity, and learning. Although many studies have examined behavioral trial-to-trial variability throughout development, there is very little information about how different forms of neural variability change throughout development and coincide with specific critical periods or developmental milestones [67]. Characterizing neural variability throughout the lifespan is, therefore, crucial for answering fundamental outstanding questions (Box 2) regarding the potential beneficial and maladaptive roles of variability in maintaining performance reliability and enabling performance flexibility.

Box 2. Outstanding questions

- How stable are neural variability measures across different brain systems and over time (e.g., hours or days) within an individual?
- How do neural and behavioral variability develop throughout the lifespan? What are the age-appropriate limits of beneficial variability, beyond which variability becomes maladaptive?
- To what extent can behavioral and pharmacological manipulations alter neural variability in an individual?
- What are the behavioral consequences of having a 'noisier' brain? Are differences in specific forms of neural variability across individuals more strongly associated with differences in particular cognitive or perceptual abilities?

Although each developmental period seems to be characterized by a degree of neural and behavioral variability, excessive levels of variability appear to coincide with the presence of different neurological and psychiatric disorders such as autism. Elucidating the spatial, developmental, and temporal aspects of within-subject variability, and how the variability gives rise to different behavioral profiles and different disorders, remains to be fully determined. Characterizing different forms of neural variability in multiple patient populations may reveal crucial information about the underlying pathological mechanisms of numerous brain disorders, it may enable the development of measures for diagnosis and for tracking the efficacy of interventions, and it may lead to the development of new therapies. Put simply, having a 'noisy' brain is likely to have considerable consequences for an individual's cognitive and perceptual abilities as well as their clinical state. Characterizing different forms of within-subject variability, and understanding how they change throughout normal and abnormal development, is therefore a promising avenue for further basic and clinical research.

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