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The development of a noisy brain

A.R. McINTOSH[1], N. KOVACEVIC[1], S. LIPPE[2], D. GARRETT[1], C. GRADY[1], V. JIRSA[3]

[1] Rotman Research Institute of Baycrest Centre, University of Toronto, Ontario, Canada;
[2] Centre de Recherche CHU Ste-Justine, University of Montreal, Canada;
[3] Theoretical Neuroscience Group, Institut des Sciences du Mouvement UMR6233 CNRS, Marseille, France & Center for Complex Systems and Brain Sciences, Florida Atlantic University, USA

ABSTRACT

Early in life, brain development carries with it a large number of structural changes that impact the functional interactions of distributed neuronal networks. Such changes enhance information processing capacity, moving the brain from a deterministic system to one that is more stochastic. The evidence from empirical studies with EEG and functional MRI suggests that this stochastic property is a result of an increased number of possible functional network configurations for a given situation. This is captured in the variability of endogenous and evoked responses or "brain noise". In empirical data from infants and children, brain noise increases with maturation and correlates positively with stable behavior and accuracy. The noise increase is best explained through increased noise from network level interactions with a concomitant decrease of local noise. In old adults, brain noise continues to change, although the pattern of changes is not as global as in early development. The relation between high brain noise and stable behavior is maintained, but the relationships differ by region, suggesting changes in local dynamics that then impact potential network configurations. These data, when considered in concert with our extant modeling work, suggest that maturational changes in brain noise represent the enhancement of functional network potential – the brain's dynamic repertoire.

Key words

Neural networks • Noise • Development • Maturation • Multi-scale entropy

In thinking about brain network function and how it enables mental function, there are several obvious things to consider. First is the structural connectivity of the system. The brain's wiring pattern is consistent with a small-world network with dense local connections and more spare distal connections (Bullmore and Sporns, 2009). Other features that have emerged include the presence of certain regions that act as hubs, connecting different local territories of specialized processing (Hagmann et al., 2008; Honey and Sporns, 2008). On top of the anatomical architecture, one would need to consider which brain areas are active at a particular time and how the sequence of activations proceeds for a given operation. After considering activation, comes co-activation, wherein anatomical connectivity enables activity changes in one node to influence, and be influenced by, other nodes (Horwitz and McIntosh, 1993; McIntosh, 2000; McIntosh and Korostil, 2008).

Another feature that seems less obvious in this consideration is "noise" that exists in these networks (Faisal et al., 2008). At one level, noise reflects the imprecision of the cellular operations within an ensemble (e.g. ion channel opening and closing, membrane fluctuations). At a second level, involving connections between ensembles, variations in transmission timing exist, which can affect the synchrony between ensembles.

Corresponding Author: Anthony Randal McIntosh, Rotman Research Institute, Baycrest, 3560 Bathurst Street, Toronto, Ontario, M6A 2E1, Canada - Tel: (416) 785 2500 ext 3522 - Fax: (416) 785 2862 - Email: rmcintosh@rotman-baycrest.on.ca

There is yet another level of noise that needs to be considered here. Linear systems are limited in their dynamics to the expression of exactly one behavior only, which is obscured in the presence of noise. Nonlinear dynamic systems, of which the brain is a prime example, have the ability to express multistability and hence multiple behaviors (Kelso, 1995; Haken, 1996). In such systems noise contributes directly to the spatiotemporal pattern formation of network configurations. The computational aspects of this are discussed in some detail in the accompanying paper in this issue (Jirsa et al., this issue). In general terms, the brain usually operates at the "edge of criticality" between any number of possible states, or functional network configurations. In the absence of noise, there is little capacity for the system to explore these states, and a potential for the system to settle into a single state. With noise, the system approaches one state and then, with noise fluctuations, may move towards another state. Hence the mutual presence of nonlinearity and noise is an absolute necessity for an exploratory dynamics to occur spontaneously in the absence of external stimulation. Around a stable anatomical skeleton, a number of potential functional configurations may be possible and the presence of noise allows access to these configurations. The combination of noise and potential network configurations results in variation in how the system will reconfigure in response to an external stimulus. It is in this sense we wish to understand "brain noise" in the current context: brain noise is an expression of the degree of variation found in brain signals, which are generated by the deterministic and random components of the brain network processes.

If these theoretical statements have validity, one would expect brain noise to change as the brain matures and ages. Maturation brings the refinement of anatomical connectivity through changes in myelination and local pruning of connections, and with experience, further development of potential functional networks (Fuchs et al., 2007). If noise is beneficial for normal function of brain networks, then there should be a positive correlation between the amount of noise present in a network and cognitive performance. In the sections that follow, we review empirical evidence that provides support for this theory from three studies: two EEG studies of infants and children, and one functional MRI study of young and old adults. We hypothesized that early maturation may lead to an increase in brain noise. While most would expect that old age would bring even more noise to the system, with the biophysical changes such as white matter loss, we speculated that advanced aging would result in a reduction of brain noise.

How do we assess "brain noise"?

The simplest method to assess noise is to look at the variance of the signal. For our fMRI study, this was done by calculating the standard deviation of the signal fluctuation across the time series for each brain region/voxel (Garrett et al., 2010). With the appropriate preprocessing steps to eliminate measurement artifact, one would assume that a physiologically noisier signal would have a higher standard deviation.

A more comprehensive method for assessing noise based on variance is to apply a principal components analysis (PCA) to single trials of a system's response to a stimulus. Since PCA is sensitive to the variance of a data set, one would assume that noisy systems should have higher variance and thus would require more principal components, or dimensions, to summarize the variance structure. A simple assessment of noise would be to compare the number of components needed to capture the same proportion of variance between different scenarios (e.g., people, tasks, etc.).

The final measure looks at temporal predictability in a time series. This measure is known as multiscale entropy (MSE, Costa et al., 2002b; Costa et al., 2005). Here the approach involves computing sample entropy of a time series, and then successively down-sampling the time series and plotting entropy as a function of temporal scale. MSE assigns low values to both highly deterministic and completely random signals, making it an explicit measure of signal complexity (Costa et al., 2002a). The method is related to spectral power analyses, but is sensitive to the temporal dependencies within a signal unlike spectral power distribution (McIntosh et al., 2008). The benefit of MSE measures is that it takes advantage of the potential that predictability depends on the temporal scale. However, the measure requires a long time series of ~500 data points to adequately

capture this scale dependency. As such, we have not been able to apply it consistently across all our studies, particular fMRI data where the time series length are usually shorter relative to EEG.

An important clarification here is that while these three measures are sensitive to different aspects of the brain signal, at present we take the liberty of considering them all as measures of brain noise. We acknowledge that this is not ideal, as noise has different implications at different levels of the system. However, further differentiation is not needed for the purposes of the points in this paper, but we shall revisit this issue in the discussion.

Face processing in children

The first study examined the relationship between maturation and brain noise in children (8-15 years) and young adults (20-33 years) (McIntosh et al., 2008). The data came from an ERP examination of responses to faces. Participants were shown a single image of a face, either normal view, contrast reversed or rotated 180º. Each trial started with a presentation of a novel or familiar face, and subjects responded by pressing either a target or a nontarget button depending on whether they recognized the face. For each subject we calculated two response time related measures: mean response time (mean RT) and coefficient of variation of the response time (cvRT). The coefficient of variation of RT was calculated as the standard deviation divided by the mean RT within subject, and was taken as a measure of subject's behavioral variability. The scaling procedure in cvRT minimizes differences between groups that arise from differences in mean and standard deviations. As a third behavioral measure, we used subject accuracy (percent correct responses), calculated from all recorded trials. The results from these measures are depicted in Fig. 1a. Behaviorally, all age groups showed high accuracy in the task, with adults near ceiling. Recognition accuracy for children, while lower than for adults, was well above chance. Mean RT was much slower for children 8-11 years and similar for children 12-15 years and adults. Importantly, cvRT showed a gradual age-related decrease.

The average evoked response to a single face showed the highest amplitude in the youngest children, and progressively decreased with age Fig. 1b. In addition, the latency of the initial response decreased with age. These two features, the change in amplitude and latency, have been well-characterized in the literature (Itier and Taylor, 2004). The bias in children towards higher amplitude, but slower, electrophysiological signals is paralleled by a differential distribution in prestimulus, or baseline, spectral power (Fig. 1c). Across age, there was a gradual reduction in low frequency spectral power and a relative increase in power at higher frequencies. The relative change in spectral power density presumably underlies the reduction in the latency of the evoked responses and its multicomponent nature, where the lower frequency bias in children would yield slow and broad evoked potentials. The emergence of higher frequencies with maturation would both decrease the evoked response latency and allow additional deflections to emerge (i.e., N100, P200, etc.).

As shown in Fig. 2a, PCA dimensionality estimation pre-stimulus and post-stimulus was highest for adults across the entire scalp. Interestingly, a comparison of pre- vs. post-stimulus PCA suggests some dimensionality reduction coming from the processing of the stimulus, which is evidenced by a reduction in PCA dimensionality post-stimulus. This is consistent with recent work that suggests stimulus onset can reduce the variability of neuronal responses throughout the cortex, but that ample variability remains (Churchland et al., 2010). In the present case, the magnitude of dimensionality gradually decreased as a function of age. This difference suggests that, with maturation, noise in the brain signals increased while the degree to which this variability was affected by incoming stimuli decreased.

MSE estimation applied to single trial data for each channel showed that sample entropy measures increased with age, with the intermediate age groups falling along an ordinal trend (Fig. 2b). While the changes occurred across most temporal scales, the effect was strongest in the middle range of the temporal scales from ~5-9.

The final and most important part of this investigation was to relate behavioral variability and brain variability during maturation. We addressed these issues by analyzing the correlations between our measures of dynamical variability (pre and post-PCA dimensionality and MSE) and overt behavior (RT-variability, accuracy and age). We also includ-

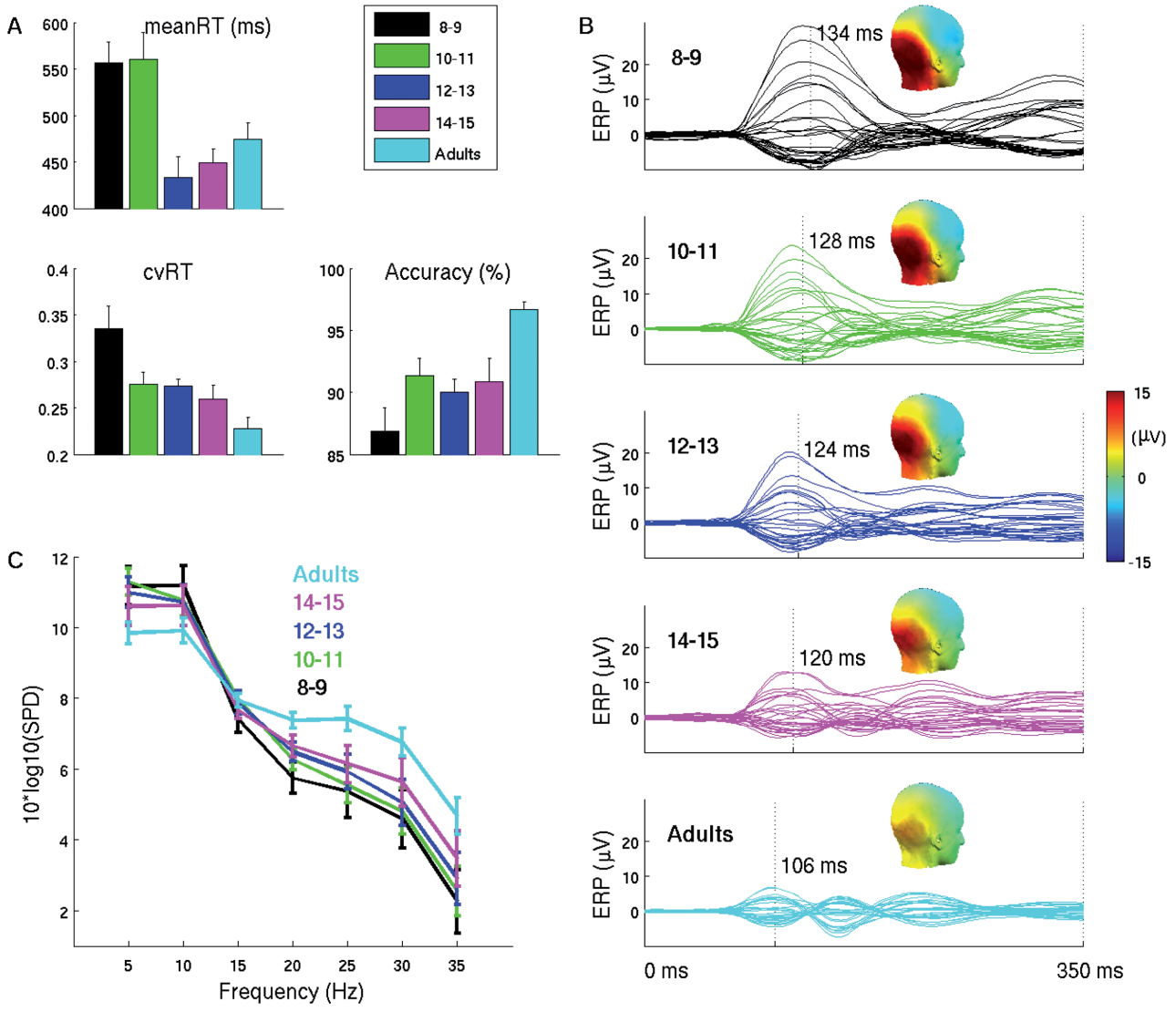

Fig. 1. - Behavior and EEG data by age (A) Behavioral results for mean RT, coefficient of variation (cvRT) and accuracy (percent correct responses). Error bars indicate group standard errors. B) Waveforms for group average ERPs across all electrodes, together with corresponding P100 latencies (marked by vertical dashed line) and P100 scalp maps. C) Group average results for spectral power distribution (SPD) during baseline interval for electrode O2. Error bars indicate group standard errors. Similar pattern was present at all channels. With maturation, decreases were observed in lower frequencies (< 10 Hz) combined with increase in higher frequencies (> 10 Hz).

ed mean RT in the analysis to determine whether the correlation patterns we observed were specific to behavioral measures of variability, or to any metric. Fig. 3 shows the results of the analysis. Computed across all subjects, the correlation between behavioral variability (cvRT), and brain variability (PCA dimensionality and MSE) was negative and highly robust across most of the EEG channels (Fig. 3a). The correlation for accuracy was a mirror image of the pattern for cvRT, showing a positive correlation with PCA and MSE estimates (Fig. 3b). Mean RT, however, showed a much weaker, and statistically unreliable, correlation pattern with brain variability measures (Fig. 3c). Finally, the correlation of chronological age and brain variability was very strong and positive across most of the scalp. Measures of behavioral consistency (cvRT and accuracy), and chronological age showed stable correlations with brain variability measured with PCA and MSE. Mean RT, however, did not. In other words, increased brain variability during maturation was associated with more stable and accurate behavior, but not necessarily faster responding.

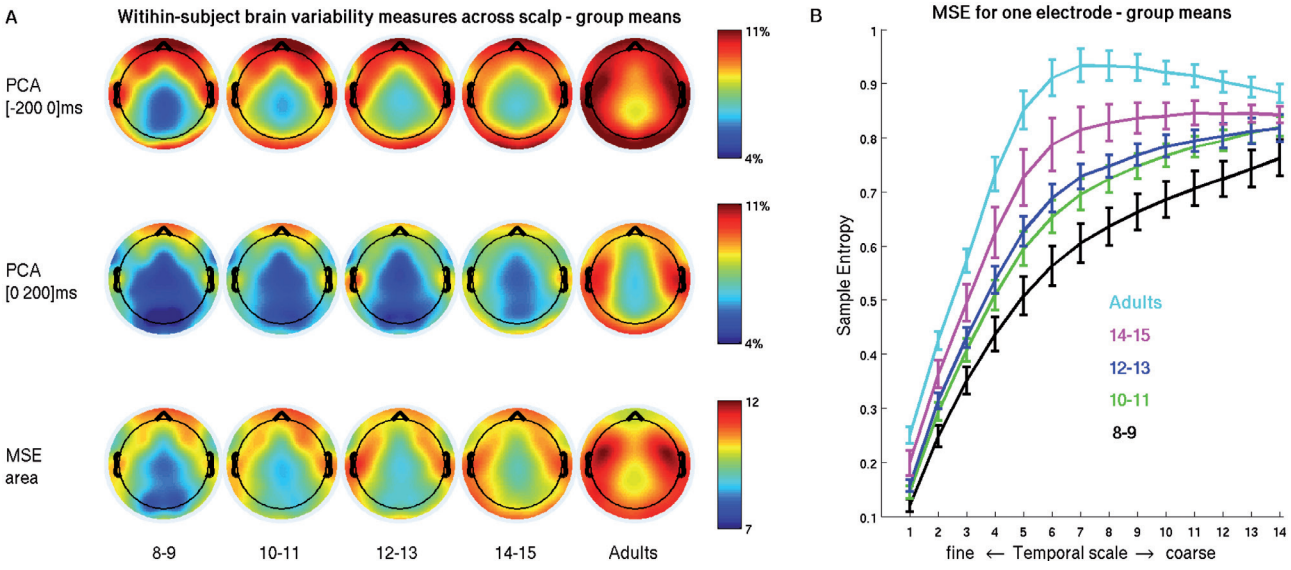

Fig. 2. - Within-subject brain variability measures across age groups. A) shows group mean results across the scalp for pre- and post-stimulus PCA dimensionality estimate of trial-to-trial variability (top two rows) and MSE area under the curve (bottom row). Scalp maps of group means were obtained by interpolating values from single channel group mean values. Gradual increase in all three brain variability measures across age groups is evident. B) shows group means for MSE estimates across temporal scales for channel O2, together with corresponding standard errors. Similar entropy curves were obtained for all channels and showed maturation-related increase in entropy at all scales. Given consistent age-related differences at all time scales, the area under the MSE curve was taken as a summary measure of maturational changes in entropy (e.g., (A), bottom row).

In the sample we studied, a maturational increase in brain noise covaried with an increase in behavioral stability. Subjects with higher signal variability showed less variability in response latency (measured with cvRT) and greater performance accuracy. Interestingly, when the measures were adjusted for the chronological age, the relationship between brain and behavioral variability weakened, but was not abolished, suggesting that only part of this relationship represented a maturational effect. It is worth reiterating that mean reaction time, which also showed a maturational change, did not significantly correlate with brain variability. It may be that other physiological factors are more important for response speed changes during maturation. By contrast, strong correlations with behavioral consistency indicate that cvRT and accuracy are likely tapping into aspects of behavioral tuning, which are more tightly related to the changes in brain variability.

These initial data confirm that brain variability increases and behavioral variability decreases with maturation. With maturation comes specialization of brain regions, but with concurrent increased integration between distributed neuronal populations and establishment of new functional connections (Johnson, 2001). The change in balance between segregation and integration would produce more variability in on-going activity, given that the number of simultaneous processes possible at any given moment increases. Mature and integrated nervous systems generally have more prolonged and complicated neural transients (Friston, 1997). Such transients are characteristic of a system with high neural complexity (Tononi et al., 1994).

Brain noise in infants

We continued to explore the relationship between brain variability in maturation by looking at infants and children in an ERP study examining the response to visual and auditory stimuli (Lippe et al., 2009). In the study, 35 children (27 days to 5 years) and 10 adults (age range 20-30 yrs) had ERPs measured during passive auditory and visual stimuli. The auditory stimuli were broadband white noise samples, and visual stimuli were reversing checkerboard patterns. Two questions were addressed: 1) whether

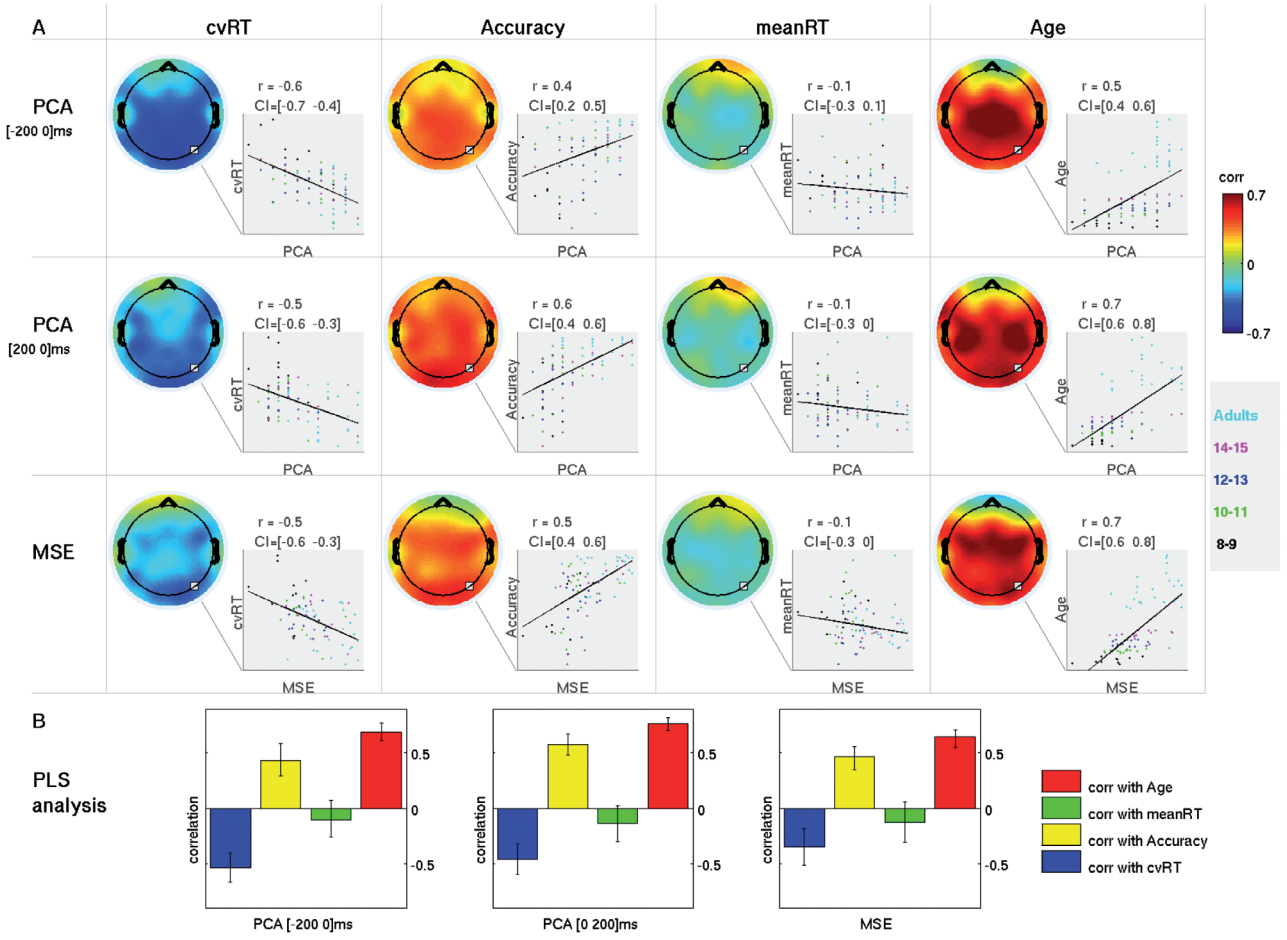

Fig. 3. - Within-subject brain variability in relation to behavior and chronological age. A) Correlations are arranged in a table where rows represent three within-subject brain variability measures (pre- and post- stimulus PCA and MSE) and columns represent behavioral measures (cvRT, accuracy and meanRT) and age. Each entry in the table shows a scalp map resulting from interpolated values from single channel correlations between given brain variability measure and given behavior or age. Unstable correlations (where the 95% CI included 0) were set to 0. Colormap corresponds to [-0.7-0.7] range of correlation values. Along with each scalp map of correlations, there is an inset showing a scatter plot representing subject measures for a single channel (electrode O2). Subjects are grouped by color according to age group membership. Estimated value of correlation (r) along with the associated 95% CI is given on top. B) Results of a multivariate statistical analysis of the observed correlations (McIntosh and Lobaugh, 2004). The bar graph plots the global correlation of brain variability and each behavior measure or age (± bootstrap estimated standard error). As can be seen, for all three brain measures there was a similar global patterns of simultaneous negative correlation with cvRT, positive correlation with accuracy and age, and no stable correlation with mean RT.

the same maturational trend observed in the first study was present in infants; 2) whether there was a differential maturational change in variability of responses in the auditory vs. visual modality.

The ERPs show the expected developmental changes in morphology, amplitude, and latency previously reported (Fig. 4, Lippe et al., 2007; Lippe et al., 2009). From a large positive wave, the morphology of the ERPs evolves beyond 5 years of age in both modalities. Topographical maps at peak latencies show the expected location of brain activity. The latency of the within group average visual evoked potential decreased by 52 ms. Similarly, the latency of the group average auditory evoked potential (AEP) decreased by 56 ms. The dominant AEP positive component amplitude also decreased from 2 to 5 years to adulthood.

For this study, only MSE was used to assess brain noise. The MSE curves produced within each age group are shown in Fig. 5. The MSE curve is shorter

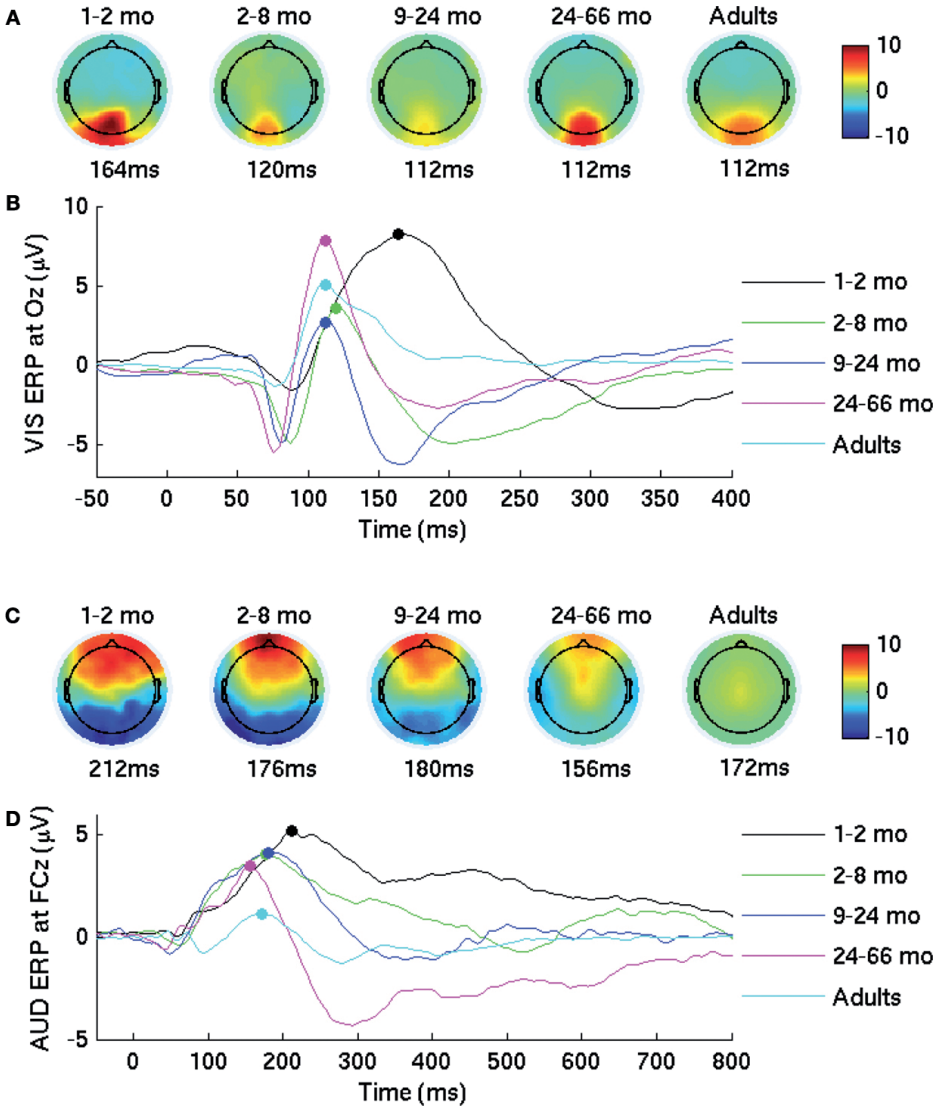

Fig. 4. - Visual and auditory evoked potentials. (A, B) Group average of the visual evoked potentials. (A) Topographies at the latency of the highest amplitude peak for each group. (B) Group average waveforms at electrode Oz. (C, D) Group average of the auditory evoked potentials. (C) Topographies at the latency of the highest amplitude peak for each group. (D) Group average waveforms at electrode FCz.

than the one derived from the previous work (Fig. 2b) because of a smaller ERP event duration. As expected, the MSE curves showed the greatest entropy for adults and the least for the youngest infants. Results confirmed a linear increase of MSE with age, regardless of the condition and of the temporal scale. The trend depicted in Fig. 2 was also present when age was treated as a continuous measure, and if the adult group is excluded from the analysis (correlations of age and MSE visual: r = 0.55, ±0.1, 95% confidence interval; auditory, r = 0.60, ±0.07 95% confidence interval).

We also tested whether MSE of auditory versus visual responses varied by age group (Fig. 6). The overall test of the interaction of MSE across groups showed significant differences between the visual and the auditory conditions by age. In fact, MSE was significantly higher in the visual condition across all temporal scales compared to the auditory condition between 2-66 months. The differences between conditions were greatest at 2-8 months, the critical period for visual system development. In contrast, MSE of auditory and visual responses could not be distinguished in adulthood. These results suggest that brain noise increases with age, but may increase differentially by sensory domain.

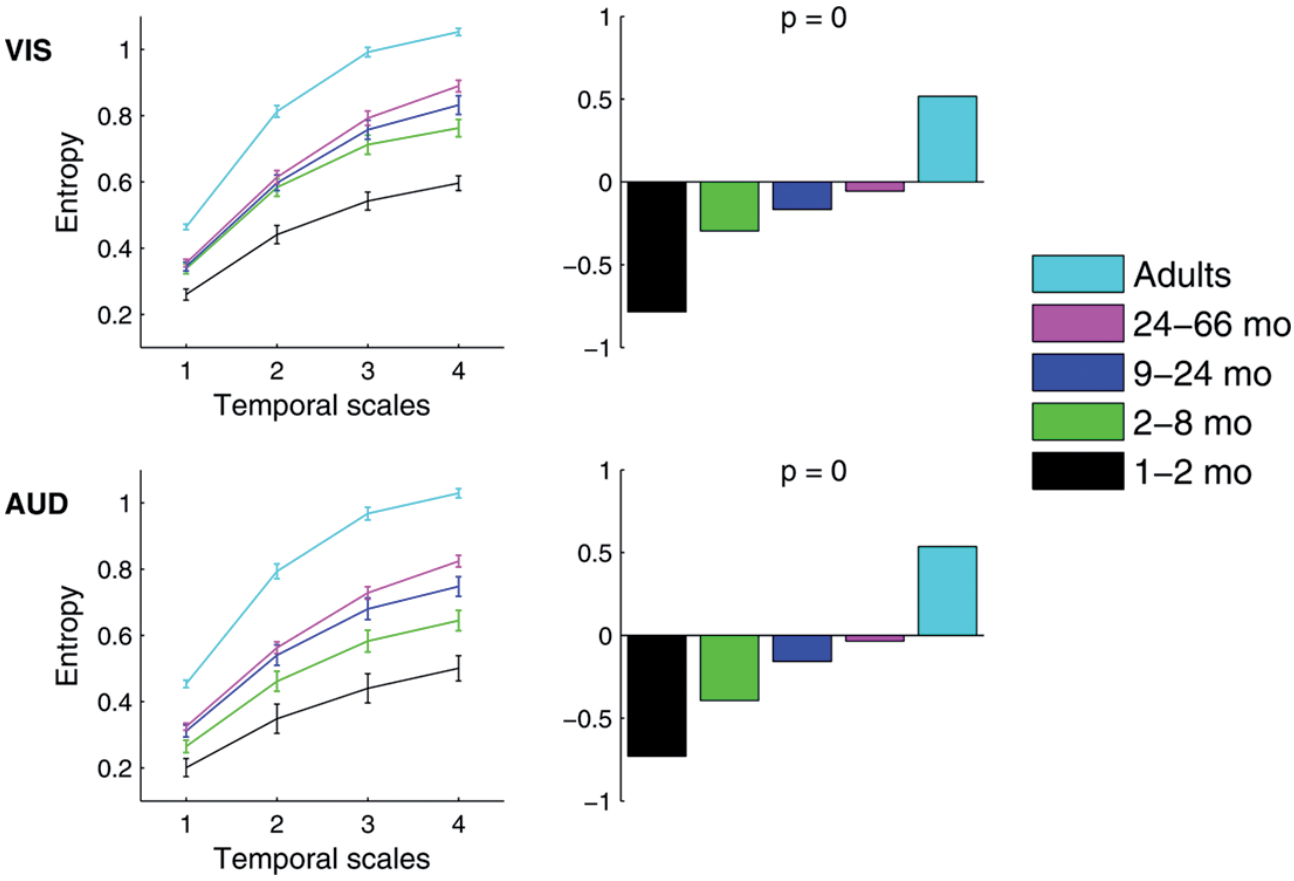

Fig. 5. - Age-related differences in multiscale entropy estimated separately in VIS and AUD conditions. Left panels show group mean entropy with error bars representing group standard errors. Right panels show statistical contrasts representing age-related increase in entropy. Contrasts for both conditions were significant and stably expressed across all temporal scales.

Taken together, these two studies present the following conclusions. First, behavioral stability increases with maturation. This result comes as no surprise. Secondly, neurophysiological variability (measured with EEG) also increases during maturation. Finally, consistent with the hypothesis that if noise is beneficial that it should correlate with behavior, we observed strong correlation between brain noise and measures of behavior stability (cvRT and accuracy). The global increase in brain noise early in development may be related to structural modifications, which change the deterministic or random components of the network resulting in greater variation of the brain signals. At the regional level, it may correspond to the increased arborization of dendritic trees (Moore, 2002), and axons (Burkhalter, 1993), enhanced connections of interneurones (Ali et al., 2007), expression of receptors (Huang and Scheiffele, 2008) and synaptic stabilization (Hua and Smith, 2004). The changes in cell firing characteristics and synaptic potential durations may result in enhanced oscillatory capacities in the higher frequency range. At a network level, the increased noise may correspond to myelin development (Paus et al., 1999), brain region segregation (Gogtay et al., 2004), and network formation, all of which enhance binding and integration capacities (Yu et al., 2008).

Adult age-related changes in BOLD-fMRI variability

The ERP studies of children indicated that brain noise increases with maturation. Following from our original hypothesis, the next question was whether brain noise also continued to change in older age. We examined the variability in the fMRI signal (Garrett et al., 2010). We studied 19 young individu-

als (20-30 years) and 28 older adults (56-84 years). The data of interest were extracted from blocks of time where subjects fixated on a cross presented via an LCD projector in the MR scanner. In addition to the standard fMRI processing steps, we performed several additional preprocessing steps aimed at reducing data artifacts. Functional volumes were first corrected for artifacts via independent component analysis (ICA) within separate runs, as implemented in FSL/Melodic (Beckmann and Smith, 2004). Voxel time series were further adjusted by regressing out motion correction parameters, and white matter (WM) and CSF time series.

To calculate BOLD standard deviations (SDs) during fixation, we performed an additional block normalization procedure, due to the fact that large block offsets often are present from residual low-frequency artifacts. To correct mean signal offsets between blocks, the fMRI signal was normalized across all fixation blocks such that the overall four-dimensional mean across brain and block was 100. For each voxel, we then subtracted the block mean and concatenated across all blocks. Finally, we calculated voxel SDs across this concatenated mean-block corrected time series. To calculate mean signal during fixation at each voxel (to which we compared brain variability), we first expressed each signal value as a percentage change from its respective block's onset value, and then calculated a mean percentage change within each block and averaged across all blocks.

The first analysis looked at the relationship between age and signal variability, showing a very strong correlation with age. Anterior temporal and cerebellar regions showed higher SD with age, whereas medial prefrontal cortex, precuneus, and bilateral inferior frontal regions showed reduced SD with age. A similar analysis was performed on the signal mean. The regional distribution of these correlations was primarily in ventral/dorsal posterior cortices and left middle frontal regions, and showed reduced mean BOLD activity with age. However, this cor-

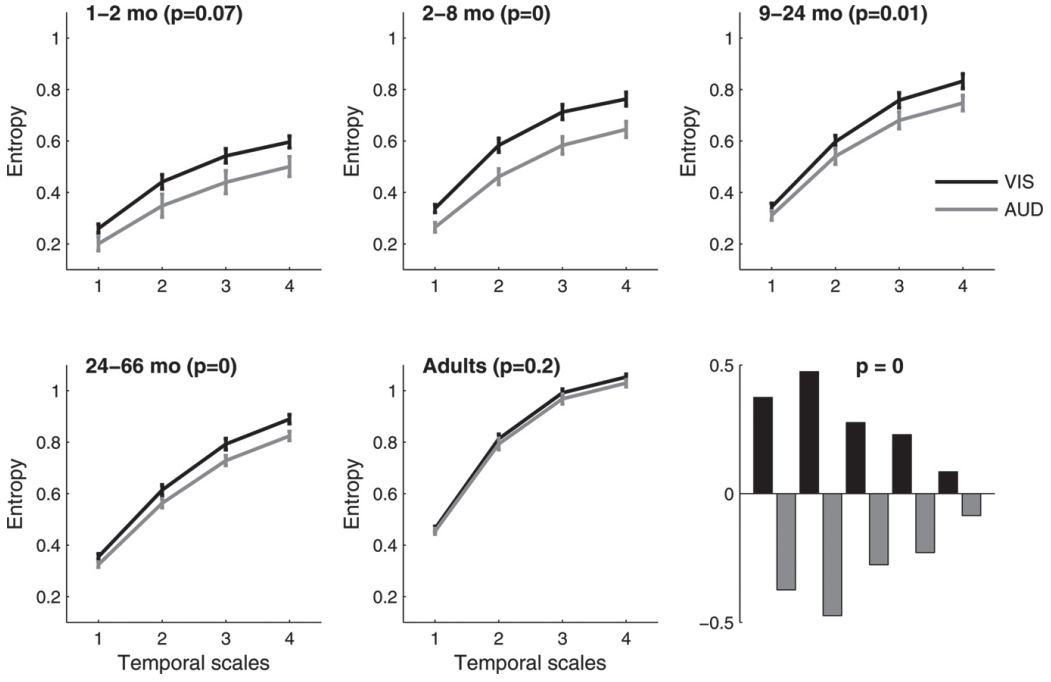

Fig. 6. - Multi scale entropy in VIS vs. AUD conditions across five age groups. Group mean entropy is shown for VIS and AUD conditions, together with group standard errors. The outcomes of the significance testing for differences in MSE between two conditions within each group are given as p values. The adult group showed no significant differences between the two conditions. Bottom right panel shows the statistical contrast between VIS and AUD conditions across all five groups simultaneously, after correcting for overall group differences. The contrast was significant and stably expressed across all four temporal scales. VIS condition exhibits higher MSE compared to AUD condition across all groups and the difference is most strongly expressed in the second group (2-8 months) in relation to other groups.

relation was weaker; compared to mean signal, SD provided more than five times the age-predictive utility. In addition, the spatial distribution of these SD differences across the brain was strikingly different from that of the mean signal (Fig. 7).

We also assessed how the SD of the BOLD signal was related to RT variability on perceptual and attentional tasks in younger and older adults. Variability in some of the areas with reduced SD in the older adults (Fig. 8), such as medial frontal cortex, precuneus and inferior frontal gyri, was associated with more variable RTs (the multivariate correlations between brain variability and RT variability ranged from 0.6 to 0.7 for all tasks, with a

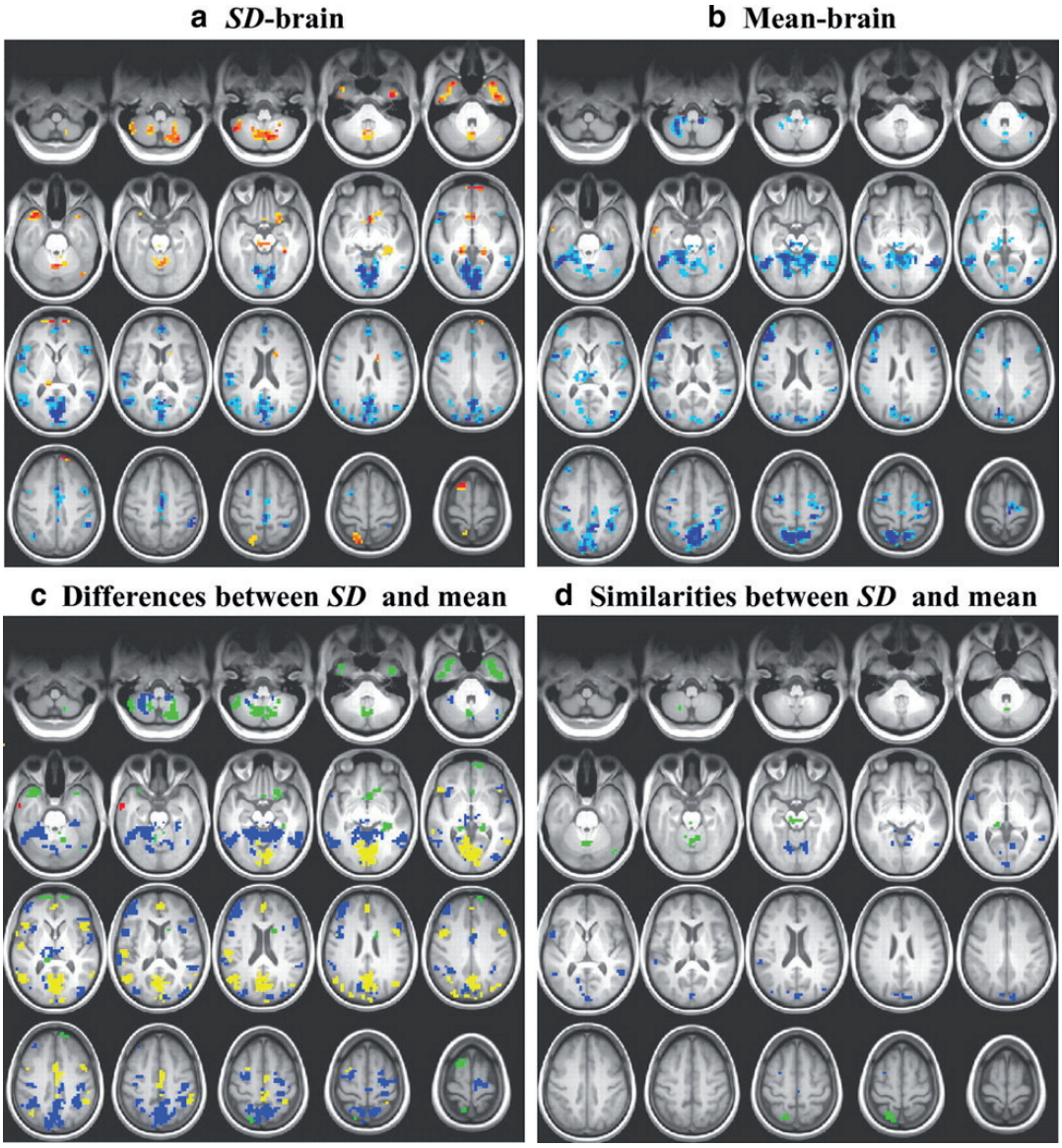

Fig. 7. - Multivariate statistical brain patterns overlay on a canonical structural MRI. a, Yellow/red regions indicate robust age-related increases, and blue regions indicate age-related decreases, in BOLD fMRI intra-individual standard deviation (SD). b, Yellow/red regions indicate robust age-related increases, and blue regions indicate age-related decreases, in BOLD means. In both a and b, all robust areas were statistically reliable with a 99% confidence interval. c, Overlay plot highlighting differences between age-based SD and mean-brain spatial patterns. Red, Mean increase, no SD effect; blue, mean decrease, no SD effect; green, SD increase, no mean effect; yellow, SD decrease, no mean effect. d, Overlay plot highlighting similarities between age-based SD and mean-brain spatial patterns. Blue, mean and SD both decrease with age; green, mean decrease, SD increase. All images represent every other slice in z-direction.

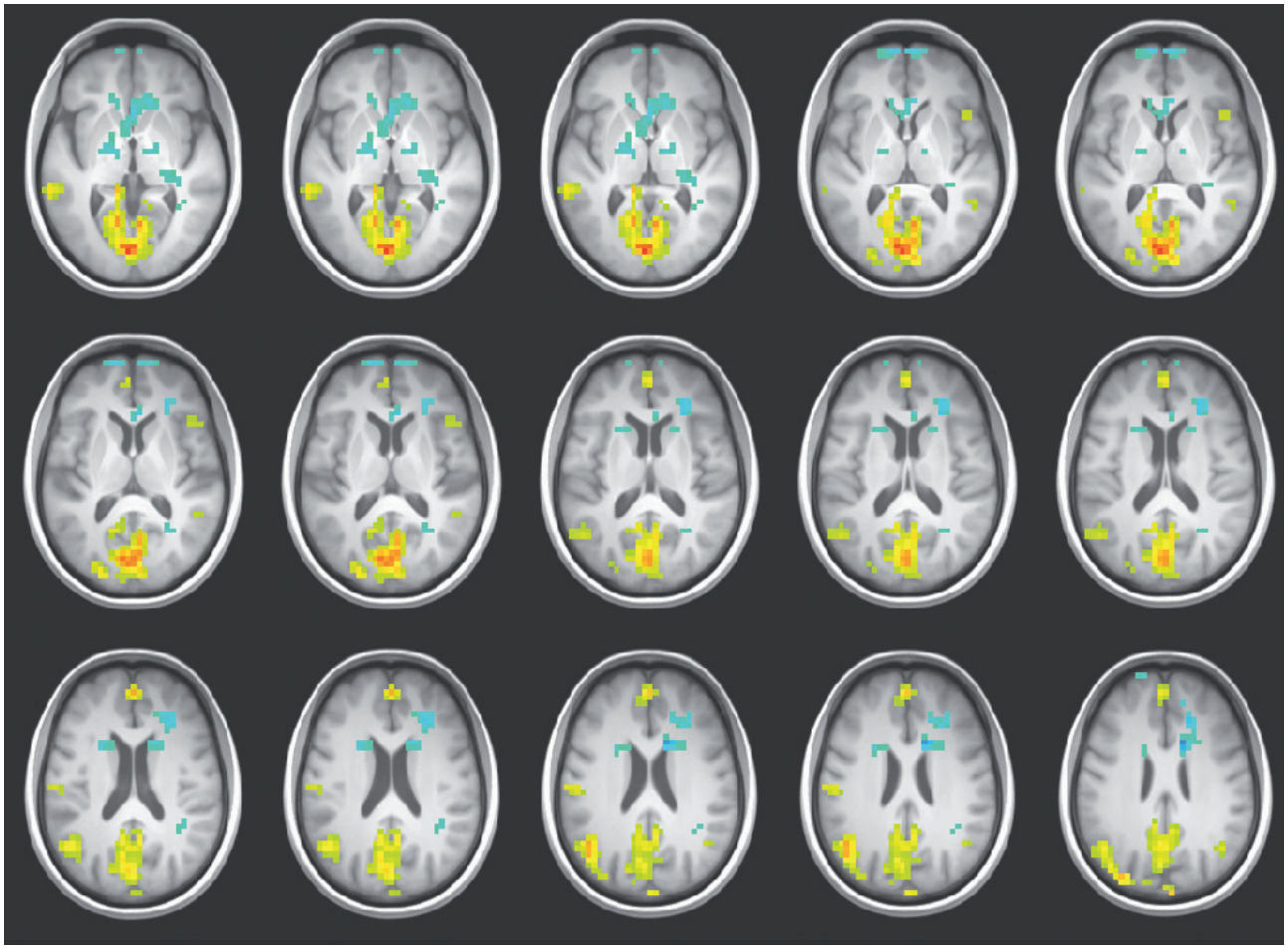

Fig. 8. - Statistical map from a multivariate analysis relating coefficient of variation in reaction time (cvRT) to the intra-individual standard deviation (SD) of the BOLD fMRI time series. Colored areas indicate regions where the relationship was statistically reliable. Regions colored yellow showed a negative correlation between BOLD SD and cvRT (i.e., higher BOLD SD, more stable reaction time), while blue areas showed a positive correlation.

stable 95% confidence interval, unpublished data). For young subjects, high variability in these regions was associated with more stable RTs. However, older adults had less variability in these areas and had more variable RTs, suggesting that regionally-specific reductions in brain noise may underlie the age differences behavior stability often reported in the cognitive aging literature.

These results partly confirm the second hypothesis we put forth, namely that normal aging results in a decrease in brain noise. Although we observed both increases and decreases in the fMRI data, the decreases were more extensive. When considered relative to the early developmental increase in brain noise, it makes sense that the degree of change may not be as global in later life. Early life experience, layered atop programmed structural changes (e.g., myelination), would result in wide-spread changes in functional networks. Even in the presence of white matter degradation and cortical shrinkage (Guttmann et al., 1998; Resnick et al., 2003; Jones et al., 2006; Raz and Rodrigue, 2006), structural changes are far less profound in older adulthood and experiential modifications more subtle; thus, the modifications of functional networks are likely more subtle.

Discussion

Collectively, the three empirical studies reviewed here demonstrate that brain noise changes with maturation and aging, and suggests that this change correlates with stable behavior. The present results

may seem at odds with the intuitive notion of behavior and brain variability, where one would expect that they go hand in hand. However, the results do make sense when the nonlinear dynamics of the nervous system are considered. Internal variability may be vital to enable the brain to parse weak and ambiguous incoming signals (Douglass et al., 1993; Traynelis and Jaramillo, 1998; Destexhe and Contreras, 2006). Variability can facilitate the exchange of signals between neurons (Stacey and Durand, 2000), transitions in metastable systems (McNamara and Wiesenfeld, 1989), and the formation of functional networks (Fuchs et al., 2007). As the nervous system matures, physiological variability increases, and the system can better adapt to its environment (Seth, 1998). In addition, as the system learns, inherent variability increases with the formation of new functional networks. Considered this way, noise enables the exploration of, and is a reflection of, the brain's dynamic repertoire.

Fig. 9 provides a useful illustration of the effect of noise in the exploration of the dynamic repertoire. On the left, we show how the trajectories of three nodes in a system approach the stable equilibrium in absence of noise by spiraling towards the fixed point. The corresponding time series display a damped oscillation. On the right, the same dynamic system is computationally solved in the presence of noise. Driven by the noise, the system explores the neighborhood of the equilibrium point, here the manifold. Each excursion further away from the equilibrium is followed by an oscillatory return along the manifold giving rise to the intermittent fast neurophysiological oscillations. One could imagine that, as the system matures and alternative functional configurations become possible, the shape of the manifold is altered. Thus for a given point within the manifold, nonsingular trajectories become possible. The figure conveys the behavior of a simple three node network, but as the complexity of the network increases through additional nodes and functional networks, one can envision a more complicated manifold with multiple co-existing régimes of attracting and repelling subregions, each of which displays different dynamic (oscillatory, transient, chaotic, etc.) behaviors.

Brain networks generally possess small-world construction, wherein there are multiple routes for different network elements to interact (Sporns and Zwi, 2004). In the presence of noise, the system will visit these network configurations spontaneously. In this case, the noise provides the *kinetic energy*

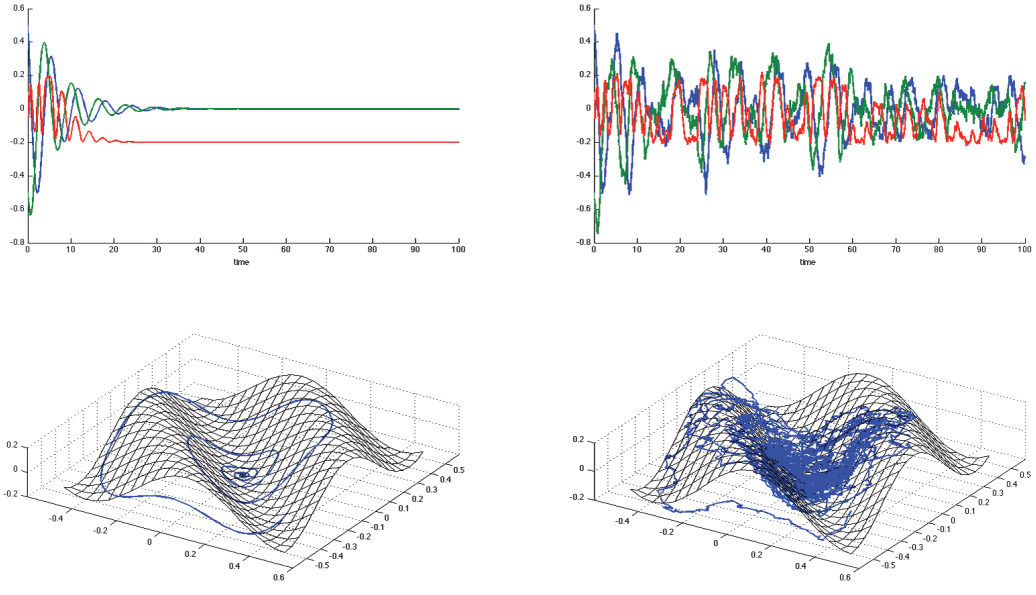

Fig. 9. - The dynamics of a simple three-node network to illustrate the exploration of dynamic range in the absence (left) or presence (right) of noise. The top figures showed the simulated time series for the three nodes and, below, the corresponding phase plots. See text for further description.

for the network to explore possible functional architectures, which gives rise to variability in the measured network dynamics. It seems reasonable to link this behavior to the notion from Bayes models of the brain (Pouget et al., 2003; Knill and Pouget, 2004). By being in a constant state of exploration, the brain can generate predictions about the likely network configuration that would be optimal for a given input. The variation of predictions is driven both by noise at the local level and by the range of functional network configurations available. The supposition is that being in the state of exploration allows the brain to deal with the ambiguity in the environment by converging on a space of potential functional configurations for a given situation. As the system converges to a response, the noise also acts to allow rapid switching of configurations once the response is generated or if the situation changes during the response execution (e.g., a draft of wind during swinging a golf club) (Milton and Mackey, 2000). Thus, optimal noise in brain networks seems to allow for more stability of the overt behavioral response (Manoel and Connolly, 1995).

Our modeling work presented in this issue (Jirsa et al.) demonstrates the importance of noise in producing the spatiotemporal dynamics that underlie resting-state in the primate brain. A key observation is that the emergence of these dynamics is critically dependent on anatomical connectivity and local noise. In early development, it stands to reason that both factors are changing, explaining the global changes in measured brain signal variability. With normal aging, noise changes are nonuniform and seem to show some regional and temporal specificity. At the regional level, some areas increase in variability and others decrease. The significance of this requires more detailed investigation, but it is possible that normal aging may bring a reduction in the variability during exploration of functional network configuration, but also increase the variability of local networks.

Given that brain noise seems to evolve during maturation to some optimum level, one may postulate that further increases or decreases, coming from disease or damage would compromise behavioral stability. In other words, noise may show changes in some pathological conditions. In disorders such as schizophrenia there appears to be too much noise, making it difficult for networks to efficiently integrate external perturbations into on-going network exploration (Winterer et al., 2000). On the other hand, a recent report on pediatric traumatic brain injury (TBI) observed that the temporal variability of phase synchronization among EEG electrodes increased as patients recovered and emerged from coma (Nenadovic et al., 2008). The authors also found that temporal variability correlated with outcomes better than conventional clinical indices. Some of our recent work noted a similar trend in adult TBI, wherein those that exhibited better behavioral recovery on an attention task showed greater brain noise (Raja et al., 2007). While this certainly is not meant to suggest that clinical conditions can be entirely explained through changes in brain noise, it does suggest that brain dysfunctions produce noise patterns that can be differentiated from the normal range. In general, the noise estimation methods we use are easily applied to clinically-relevant neuroimaging tools (e.g., EEG and fMRI), and thus could increase the sensitivity for detection of brain network changes. Moreover, under the assumption that optimal noise is a signature of optimal brain function, monitoring brain noise may be a sensitive marker of recovery of function and potentially of clinical outcome.

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