Brain noise is task-dependent and region-specific

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The emerging organization of anatomical and functional connections during human brain development is thought to facilitate global integration of information. Recent empirical and computational studies have shown that this enhanced capacity for information processing enables a diversified dynamic repertoire that manifests in neural activity as irregularity and noise. However, transient functional networks unfold over multiple time scales and the embedding of a particular region depends not only on development, but also on the manner in which sensory and cognitive systems are engaged. Here we show that noise is a facet of neural activity that is also sensitive to the task context and is highly region-specific. Children (6-16 years) and adults (20-41 years) performed a one-back face recognition task with inverted and upright faces. Neuromagnetic activity was estimated at several hundred sources in the brain by applying a beamforming technique to the magnetoencephalogram (MEG). During development neural activity became more variable across the whole brain, with most robust increases in medial parietal regions, such as precuneus and posterior cingulate cortex. For young children and adults, activity evoked by upright faces was more variable and noisy compared to inverted faces and this effect was reliable only in the right fusiform gyrus. These results are consistent with the notion that upright faces engender a variety of integrative neural computations, such as the relations among facial features and their holistic constitution. The present study demonstrates that transient changes in functional integration modulated by task demand are evident in the variability of regional neural activity.

Keywords: variability, noise, development, face inversion

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1 Introduction

The refinement of structural connections during brain development leads to an increasingly sophisticated neural architecture in which local segregation and global integration are reconciled to confer the greatest possible capacity for information processing (Tononi et al. 1994). At first blush it is difficult to imagine how ostensibly “noisy” neural activity arises from such an intricate arrangement. Yet this very unpredictability and irregularity may be the product of a nonlinear dynamical system that is exploring its functional repertoire around its anatomical frame (Ghosh et al. 2008).

As communication between distributed neuronal populations intensifies relative to short-range, “local” communication (Fair et al. 2009; Supekar et al. 2009), the developing brain gradually becomes increasingly capable of functionally integrating information from segregated regional sources (Johnson 2001). In the mature integrated brain the unique balance between differentiation and specialization leads to a system with high neural complexity (Tononi et al. 1994), which enables an increased number of simultaneous processes and metastable states and gives rise to on-going activity with greater information content. The information content of neural activity can be captured by a variety of entropy-based metrics that quantify the variability of the signal (Richman and Moorman 2000). Recently, the variability of brain signals has been used to track development and to show that it is characterized by progressively greater departures from regularity (Meyer-Lindenberg 1996; Anokhin et al. 2000; Fuchs et al. 2007; McIntosh et al. 2008; Lippé et al. 2009). Moreover, this trend correlates with more stable and accurate behavior (McIntosh et al. 2008).

However, it seems unlikely that variability is a static facet of neural activity. Transient functional networks emerge and disappear over multiple time scales (Honey et al. 2007), reflecting momentary interareal associations that allow information to be integrated. Thus, the embedding of a particular region in such networks (its “neural context”, see (McIntosh 1999; Bressler and McIntosh 2007)) must be fluid and highly sensitive to the manner in which sensory and cognitive systems are engaged at the time. The main goal of the present study is to show that modulation of functional integration during a cognitive task manifests in neurophysiological activity as systematic changes in variability. In addition, structural and functional connectivity, metabolic characteristics and developmental trajectories all vary among brain regions (Taylor 2006). Therefore, task- and age-dependent changes in brain signal variability should also be spatially heterogeneous.

To study the regional specificity of signal variability, we used the MEG in conjunction with a beamforming technique (Robinson and Vrba 1999; Sekihara et al. 2001; Cheyne et al. 2007) to estimate activity at several hundred sources distributed evenly in the brain (Fig. 1) while children (6-16 y) and adults performed a face recognition task with upright and upside-down (inverted) faces. We hypothesized that age-dependent increases in variability should be observed across most of the brain, since in the age range of our sample almost all cortical areas are subject to some degree of myelination and synaptic pruning (Lenroot and Giedd 2006; Paus et al. 1999). However, if the variability of regional signals reflects their participation in emerging structural and functional networks,
then the greatest age-dependent increases should be observed in areas that are highly interconnected with the rest of the cortex and that occupy central positions (Hagmann et al. 2008) in multiple such networks.

A face recognition task allowed us to examine whether signal variability is task-dependent. We took advantage of the face inversion effect, whereby the recognition of faces is impaired when they are presented upside-down. Although a similar effect is observed for other types of visual stimuli such as everyday objects, the extent of the impairment is disproportionately large for faces (Yin 1969). Several theories posit how the processing of upright and inverted faces differs, including the importance of configural (Freire and Lee 2001; Rhodes et al. 1993; Mondloch et al. 2002) and holistic (Farah et al. 1995; Tanaka and Farah 1993) information. For the present purposes, we merely note that nearly all research to date suggests that there are significant differences in the way in which inverted and upright faces are processed, both in adults and in children. We hypothesized that if faces presented upright engender greater integration of information about the relations among features as well as their overall arrangement, then brain signals evoked by upright faces should be less predictable.

2 Materials and Methods

The temporal predictability of neural activity was indexed using multiscale entropy (MSE), which is calculated by down sampling single trial time series to progressively coarse-grained time scales and calculating sample entropy ($S_E$) at each scale (Costa et al. 2005). Compared to other measures of variability, MSE can be used with relatively short time series. Moreover, as an entropy-based measure, MSE is explicitly sensitive to the information content of a signal and will assign low values to completely deterministic and uncorrelated random signals alike. Finally, the multiscale nature of the index takes into account the fact that physiological dynamics underlying the expressed information are likely to unfold over multiple temporal scales (Honey et al. 2007).

We sought to identify spatial patterns of task-dependent changes in variability that were expressed across multiple age groups, without an a priori region of interest. Thus, we opted for a multivariate analytic approach (partial least squares, PLS) (McIntosh and Lobaugh 2004) which allowed us to statistically assess group and task differences simultaneously across all sources and temporal scales. To ensure that the effects we report cannot be explained by well-known changes in averaged evoked neuromagnetic responses due to maturation or face inversion, we also computed MSE on single trials from which the subject- and condition-specific average event-related fields (ERFs) had been subtracted. If MSE is sensitive to non-deterministic properties of the signal, then it should not be affected by the subtraction of the evoked response. Previous studies suggest that changes in MSE tend to closely follow changes in spectral power (McIntosh et al. 2008; Lippé et al. 2009), but that they offer complementary information about the signal (Gudmundsson et al. 2007; McIntosh et al. 2008). To this end, we also computed power spectral density (PSD) for all trials. Thus, in one set of analyses we examined changes in $S_E$ across sources and temporal scales and in the other we looked at changes.
in PSD across sources and frequency bands.

2.1 Participants

Seventy-one naïve, healthy participants took part in the study, including 49 children, aged 6-7 (n=10, 3 female), 8-9 (n=10, 9 female), 10-11 (n=9, 2 female), 12-13 (n=10, 6 female), 14-16 (n=10, 3 female) and 22 adults, aged 20-41 years (mean age 25.7 years, 9 female). None of the participants wore any metallic implants or had metal in their dental work. All participants reported normal or corrected-to-normal vision. Experiments were performed with the informed assent and consent of each individual (or the signed consent of the parents of participants younger than 16 years) and with the approval of the Research Ethics Board at the Hospital for Sick Children.

2.2 Stimuli and Task

Participants performed a one-back task in which they indicated whether the currently-viewed stimulus was the same the previous one. The stimulus set comprised 240 greyscale photographs of faces of young adults (2.4 x 3° visual angle) with neutral expressions that were unfamiliar to the participants. All faces were without glasses, earrings, jewelry or other paraphernalia. Male and female faces were equiprobable. In each block of trials, one third of the faces immediately repeated, resulting in 120 new faces and 60 repeated faces (180 total) per block. To avoid confounding effects of memory, we only analyzed trials that contained new faces. Upright faces were presented in one block and inverted faces in the other, with the order of the two blocks counterbalanced across participants. Stimuli were back-projected via two mirrors to a screen positioned at a viewing distance of 70 cm from the participant. Faces were presented centrally over a uniform black background for 500 ms. The duration of the inter-stimulus interval was varied randomly and with equal probability between 1200 and 1500 ms and a white fixation cross was displayed throughout that time. Subjects were instructed to respond as quickly and accurately as possible whenever a face was repeated. Triggers were generated by a photodiode that directly measured the time of stimulus onset. Stimulus presentation and responses were controlled using Presentation (Neurobehavioral Systems Inc.).

2.3 Magnetoencephalogram (MEG) Acquisition

All MEG recordings were made in a dimly-lit magnetically shielded room at the Hospital for Sick Children. Head position relative to the MEG sensor array was determined at the start and end of each block using three localization coils that were placed at the nasion and bilateral preauricular points prior to acquisition. Motion tolerance was set to 0.5 cm. Neuromagnetic activity was acquired using a 151-channel whole-head CTF system (MEG International Services Ltd.) at a rate of 625 Hz. Data were epoched into [-100 1500] ms segments time-locked to stimulus onset. Structural MRIs were also acquired for each participant. Following the MEG recording session, the three localization coils
were replaced by MRI-visible markers and 3-D SPGR (T1-weighted) anatomical images were acquired using a 1.5 T Signa Advantage system (GE Medical Systems).

2.4 Event-Related Beamforming (ERB)

ERB (Robinson and Vrba 1999; Sekihara et al. 2001; Cheyne et al. 2007) is a 3D spatial filtering technique that uses surface field measurements to estimate activity at desired locations in the brain. Individual anatomical MR images were warped into the standard Talairach space using a nonlinear transform in SPM2. 529 source locations were chosen on a grid of size 5 mm such that they were uniformly spaced and sufficiently few in number to allow reasonable MSE computation time (Fig. 1). The chosen locations were then warped back into the individual participants’ brains using the inverse transform. Activity at each target source was estimated as a weighted sum of the surface field measurements. Weight parameters and the orientation of the source dipole were optimized in the least squares sense, such that the average power originating from all other locations was maximally attenuated without any change to the power of the forward solution associated with the target source. The weights were then used to compute single-trial time series for each source.

2.5 Multiscale Entropy (MSE)

In multiscale entropy (MSE) analysis (Costa et al. 2005) each single trial time series is downsampled to multiple temporal scales and sample entropy ($S_E$) (Richman and Moorman 2000) is calculated for each scale. For a given temporal scale $\tau$, the corresponding time series is derived by averaging data points in non-overlapping windows of length $\tau$ from the original time series. The $S_E$ algorithm calculates the conditional probability that any two sequences of $(m+1)$ data points will be similar to each other given that they are similar for the first $m$ points, which reflects the degree of regularity in a given time series. The $S_E$ metric is the negative of the natural logarithm of this quantity, so higher values of $S_E$ are associated with less regular and more variable time series. In the present study, pattern length was set to $m = 2$ and the similarity criterion to $r = 0.5$. MSE was calculated for each of the 529 source locations and averaged across trials. We also wanted to confirm that group differences in the amplitude, latency and morphology of evoked neuromagnetic response did not influence MSE estimates. Therefore, we additionally selected one source in the cluster extracted from the task analysis (described below) and subtracted the subject-specific average evoked response (ERF) from the single trials prior to calculating MSE.

2.6 Power Spectral Density (PSD)

Single-trial power spectra were computed using the Fast Fourier Transform (FFT). Global signal power tends to change with age, so to capture the relative contribution from each frequency band all time series were first normalized to mean 0 and standard
deviation 1. Given a sampling rate of 625 Hz and 1000 data points per trial, the frequency resolution was effectively 0.625 Hz; the analysis was constrained to the [0.625 50] Hz range.

2.7 Partial Least Squares (PLS) Analysis

Partial least squares (PLS) analysis is a multivariate statistical technique that can be used in the context of neuroimaging to relate a set of design variables (e.g. groups and/or conditions) to a set of dependent measures of brain activity (e.g. $S_E$) that vary across one or more dimensions (e.g. space and temporal scale) (McIntosh and Lobaugh 2004). Singular value decomposition (SVD) is used to compute an optimal least-squares fit to the covariance between those sets of variables (e.g. MSE across all sources and age groups/conditions). The procedure is conceptually similar to canonical correlation, save for the fact that it is not adversely affected if the matrix is rank-deficient. Each individual solution is termed a “latent variable” (LV) and is expressed in terms of two orthogonal vectors of design saliences and source saliences, as well as a scalar singular value ($s$). In the present analysis, each LV represented one contrast between experimental groups and/or conditions (design salience) in relation to a particular pattern of sources and temporal scales that expressed that contrast (source salience). The “cross-block” covariance between the design block and brain data block that is captured by an LV is reflected by the singular value. Thus, effect size was indexed as the ratio of the square of the singular value associated with that particular LV to the sum of all squared singular values derived from the decomposition. Experimental effects captured by each LV were statistically assessed using resampling techniques.

The significance of each statistical effect was determined using permutation tests. Each permuted sample was obtained by random sampling without replacement to reassign the order of conditions within participants (500 replications). The $p$-value was determined by calculating the proportion of permuted singular values that was equal to or exceeded the original singular value. The stability of each statistical effect was indexed at all data points across participants using bootstrap resampling to estimate standard errors of the corresponding source saliences (Efron and Tibshirani 1986). Bootstrap samples were generated by random sampling with replacement of participants within conditions (500 replications). Saliences were deemed to be reliable across participants if the 99% confidence interval did not include zero. Under the assumption that the bootstrap distribution is unit normal, this condition holds if and only if the absolute value of the ratio of the salience to its bootstrap-estimated standard error is greater than or equal to 2.57. Statistical maps were generated using tessellation-based linear interpolation to estimate bootstrap ratios for each voxel. Bootstrap ratios were then thresholded across all data points to allow parsimonious identification of LVs.

Behavior PLS (McIntosh and Lobaugh 2004) was used to identify task-dependent changes in brain-behavior correlations. Participants’ chronological age, mean reaction time (RT), coefficient of variation of RT (cvRT) and mean accuracy were expressed as subject-specific z scores and correlated with $S_E$ across participants. The resulting correlation matrix was subjected to SVD. Significance and stability of statistical effects were
estimated using the permutation test and bootstrapping procedure described previously.

3 Results

3.1 Development

We performed two analyses of the effect of age (one for each condition) in order to examine the influence of development on signal variability. More coarse-grained samples were associated with greater $S_E$ across all participants and regions, giving rise to MSE curves with shapes similar to the ones described in previous reports (McIntosh et al. 2008) (Fig. 2a). “Coarser” scales were assigned higher $S_E$ values, although the effect of coarse-graining was greatest towards the finer scales. This characteristic morphology was preserved even when the evoked response was subtracted from single-trials (Fig. 2b).

In the first analysis participants were stratified according to their age group. The expected developmental increase in variability was reliable by bootstrap at all temporal scales. The predictability of single trial time series was highest for children aged 6-7 years and lowest for adults. The effect was observed for both inverted and upright faces ($p<0.001$ for both) (Fig. 3a) and accounted for 88.52% and 88.22% of covariance between age and $S_E$ in the respective datasets ($s=21.49$ and 21.27). This increase in variability was ubiquitous across the cortex (Fig. S1), but it was most pronounced and statistically most reliable in medial parietal cortex for both conditions (Fig. 3b).

Spectral power also followed a developmental trend, for both upright ($p<0.001$, 80.62% of cross-block covariance, $s=28.16$) and inverted faces ($p<0.001$, 81.81% of cross-block covariance, $s=27.19$) (Fig. 4a). Increased age was associated with diminished density at low frequencies ($\delta$ band) and enhanced density at high frequencies ($\alpha$, $\beta$ and low $\gamma$ bands), as evident in the frequency-wise transition from negative to positive ratios of source saliences to their bootstrapped standard errors across the whole brain at approximately 12 Hz (Fig. 4b). Both trends were most stable in lateral parietal cortices (Fig. 4c,d).

3.2 Face inversion and development

To examine the effect of face inversion on brain signal variability, runs with inverted and upright faces were contrasted across all age groups. Overall, upright faces were associated with greater variability than inverted faces in children aged 6-7, 8-9, 10-11 and in the adults, while the opposite relation held for children aged 14-16 ($p<0.001$, 37.38% of cross-block covariance) (Fig. 5a). Upright and inverted faces could not be reliably differentiated using MSE in children aged 12-13. The effect was consistent across all temporal scales and was mainly expressed by the ventral anterior portion of the right fusiform gyrus (Fig. 5b). The effect was also stable in the superior aspect of the right cerebellum, which is not uncommon in the face processing literature using data-driven source localization with MEG and is likely due to spatial smearing from inferior temporal sources (Itier et al. 2006; Taylor et al. 2008).
Inversion effects were also observed in the power spectra ($p<0.001$, 29.27% of cross-block covariance)(Fig. 6a). The pattern was similar to the results obtained using MSE, as differences were observed for children aged 6-7, 8-9, 10-11 and for the adults. Bootstrap ratios indicated that the effect was primarily driven by increased power in response to upright faces in two frequency bands: 12-15 Hz and 25-50 Hz (Fig. 6b), roughly corresponding the classical $\alpha$ and lower $\gamma$ bands, respectively. The $\alpha$ effect was expressed at most sources, while the $\gamma$ effect was constrained mainly to a region of the right inferior temporal cortex (Fig. 6c), in close proximity to the fusiform gyrus and anterior cerebellum. Upright and Inverted runs could not be differentiated by spectral density in children aged 12-13 and 14-16 (Fig. 6a).

3.3 Relation with behavior

We studied accuracy (Fig. 7a), mean reaction time (RT, Fig. 7b) and the coefficient of variation of RT (cvRT, Fig. 7c) using a mixed-factor repeated measures analysis of variance with conditions as a within-subjects factor and age groups as a between-subjects factor. Upright and inverted runs could only be distinguished in terms of accuracy [$F(1,65)=12.079, p=0.0009$], but not by mean RT [$F(1,65)=0.555, p=0.459$] or by cvRT [$F(1,65)=1.429, p=0.2363$]. However, age did affect all three measures, such that older groups produced responses that were more accurate [$F(5,65)=8.121, p=0.000005$], faster [$F(5,65)=2.484, p=0.0404$] and less variable [$F(5,65)=6.981, p=0.00003$]. The inversion effect (or lack thereof) did not appear to change with age, as no reliable interactions between age group and condition could be detected for accuracy [$F(5,65)=1.511, p=0.1986$], mean RT [$F(5,65)=0.808, p=0.548$] or cvRT [$F(5,65)=0.974, p=0.4405$].

The correlations between MSE and behavior are shown in Fig. 7d. Overall, this pattern of brain-behavior correlations was significant by permutation test ($p=0$) and accounted for 89.99% cross-block covariance. Increasing age was associated with increasing variability, for both inverted ($r=0.468$) and upright faces ($r=0.541$). The age-dependent increase in variability was associated with more accurate performance ($r=0.255$ for inverted and $r=0.337$ for upright). Interestingly, greater variability was also associated with lower cvRT ($r = -0.441$, indicating more stable performance) but this relation only held for upright faces. In contrast to task-induced differences, this effect was not specific to any particular region and was expressed by most.

4 Discussion

We have shown that the temporal predictability of MEG signals indexes changes in functional integration during a cognitive task. The present study reveals that “neural noise” is both task-dependent and region-specific. In addition, the data confirm and extend two key findings from EEG recordings: the characteristic shape of the neurophysiological MSE curve and its prominent increase in development (McIntosh et al. 2008).

Despite the fact that maturation and face inversion have a considerable effect on evoked neurophysiological responses, we have demonstrated that MSE is unaffected by
subtraction of ERFs from single trials (Fig. 2). Therefore, MSE reflects a facet of the signal that cannot be measured using the averaged evoked neurophysiological response and the effects we report are unlikely to be caused by task- or age-dependent changes in ERF amplitude, latency or morphology.

4.1 Development

The age-dependent increase in variability was manifest across the entire brain. In the age range of the present sample, the brain undergoes system-wide changes, including extensive myelination and synaptic pruning (Lenroot and Giedd 2006; Paus et al. 1999; Taylor 2006), consistent with our finding that activity from almost all areas of the brain became less predictable with increased age. The increased variability suggests a dynamical system with a broad functional scope and a multitude of metastable states (Ghosh et al. 2008). The behavioral consequences of such “noisy” activity appear to be beneficial to overall performance, as greater variability was associated with more accurate and more stable responses (Fig. 7).

Although variability increased in most parts of the brain, the increase was not homogeneous. Instead, the most marked and most reliable gains were observed in the medial posterior cortex, including the precuneus and posterior cingulate. These areas are unique because of the strategic position that they occupy in the structural hierarchy of the cerebral cortex. Recent studies have profiled the community structure of the cortex in terms of graph theoretic metrics (Bullmore and Sporns 2009). Parts of the medial posterior cortex, including the precuneus and posterior cingulate, have been identified as a putative structural core by virtue of their singular topological properties, including dense connectivity (degree), short average path length to other regions (efficiency) and participation in a high proportion of short paths between other regions (betweenness centrality), both in anatomical (Hagmann et al. 2008; Iturria-Medina et al. 2008) and in functional brain networks (Achard et al. 2006; Hagmann et al. 2008). The same areas tend to feature prominently in default-mode (Raichle et al. 2001) or task-negative (Fox et al. 2005) networks, perhaps as a direct consequence of their connectivity (Bullmore and Sporns 2009).

The role of hub regions in neural development is still unclear, but several recent reports suggest that their emergence may facilitate functional integration at the global level. Namely, in the age range similar to our sample resting state functional networks gradually reconfigure in a manner that intensifies global integration relative to local segregation, effectively shifting the balance from more local, short-distance information processing in children to more distributed processing in young adults (Fair et al. 2009; Supekar et al. 2009). The increased importance of global integration and long-distance communication implies that hub regions should play an important role in that process.

Power spectra closely paralleled previous literature, with typically weaker contribution from lower frequencies ($\delta$) and greater contribution from higher frequencies ($\alpha$, $\beta$ and $\gamma$) as the brain develops (Gasser et al. 1988). This further suggests that during development there is an increase in long-range communication (supported by low frequencies) relative to short-distance communication (supported by high frequencies). The effects could be
observed across all sources, but they were most reliable in the posterior cortex. Unlike MSE, where the age effect was medial, the effect captured by PSD was distinctly more lateral.

4.2 Face inversion and development

Signal variability was also sensitive to face inversion. The overall departure from regularity in response to upright faces is consistent with the notion that humans acquire a greater propensity for configural and holistic processing as they mature. Configural processing is the computation of second-order relations (spatial separation) among the features of a face. Holistic processing is the instantiation of a gestalt: a percept in which all discernible characteristics of a face are unified. The two modes of processing are similar in the sense that both suggest intensified interareal integration and more challenging cognitive computations and both could be disrupted by inversion (Maurer et al. 2002).

These data suggest that the irregularity and information content of neural activity reveal much more about the underlying system than previously thought. Namely, predictability of measured brain signals is not merely an invariable consequence of complex structural connectivity but also depends on transient functional networks that unfold over this anatomical foundation. The degree to which activity temporally strays from regular stereotyped patterns is related to the short-lived associations that are instantiated in the context of sensory and cognitive involvement. It has been recognized that to fully specify the participation of a particular brain region in a given task the entire profile of functional relations with the rest of the brain must be taken into account (McIntosh 1999; Bressler and McIntosh 2007). Task-modulated functional integration - indexed by signal variability - offers a unique insight into such ephemeral associations that collectively constitute the neural context.

Across age groups, these task-specific developmental trajectories were driven most strongly by the right fusiform gyrus. Functional magnetic resonance imaging (fMRI) studies have consistently linked the right fusiform gyrus to face processing by virtue of the fact that faces elicit greater blood-oxygen-level dependent (BOLD) responses compared to other types of stimuli (Puce et al. 1995; Kanwisher et al. 1997; McCarthy et al. 1997; Halgren et al. 1999; Haxby et al. 1999). In addition, some studies have found that in adults, the right fusiform gyrus is sensitive to face inversion, such that upright faces are often associated with greater activity compared to inverted faces (Kanwisher et al. 1998; Haxby et al. 1999; Yovel and Kanwisher 2005).

Why is the variability inversion effect reversed in adolescents? This observation is reminiscent of previous literature on the neural development of face processing skills. For example, the amplitude and latency of the face-sensitive N170 evoked potential follow a similar trajectory. In adults, the N170 is both more negative and occurs at a longer latency when faces are inverted (Bentin et al. 1996; Rossion et al. 1999; Itier and Taylor 2002). However, in young children this effect is largely reversed, such that upright faces are associated with greater amplitude and longer latencies (Taylor et al. 2001; Itier and Taylor 2004; Taylor et al. 2004). Similar reversals have been reported in the fMRI literature as well. In children the BOLD inversion effect is sometimes reversed and in
adolescents it is not statistically significant (Passarotti et al. 2007). We conjecture that the reversals in the inversion effect may reflect an interaction between the distinct rates of development of holistic and configural processing (Maurer et al. 2002). For example, holistic processing is reported to be fully developed by (and presumably dominant at) age six (Carey and Diamond 1994; Tanaka et al. 1998) whereas sensitivity to second-order relations is only marginally above-chance (Freire and Lee 2001; Mondloch et al. 2002) and continues to develop until late adolescence/early adulthood. The “flip” in the MSE inversion effect in adolescence could be indicative of a transition period during which the two modes contend to the overall detriment of information processing.

A similar differentiation of conditions was observed in the power spectra. The greatest contributors to the inversion effect were the young children and adults, while the difference was not reliable in adolescents. The inversion effect could be segregated into two frequency-specific components. The first was an increase in α band density in response to upright faces, which was observed across the whole brain. The second was a similar increase in density in lower γ, but this effect was spatially much more constrained and could be localized to the right fusiform gyrus.

4.3 Methodological considerations

Spectral power and MSE appear to follow similar trajectories, so how are they related? The downsampling procedure that is used to realize a multiscale representation of the signal systematically alters its spectral composition by decimating progressively lower frequencies at each subsequent temporal scale. Thus, we have to be cautious not to misinterpret changes in spectral power as changes in variability. However, the MSE trends described in the present report were reliable by bootstrap test across all calculated temporal scales and therefore insensitive to their varied spectral profile. Moreover, MSE estimates are profoundly affected if the phase structure of the signal is randomized in the Fourier domain (McIntosh et al. 2008). In other words, MSE appears to be sensitive to temporal dependencies in the signal and provides information complementary to the power spectrum (Gudmundsson et al. 2007; McIntosh et al. 2008).

The latencies, amplitudes, topographies and morphologies of face-sensitive evoked responses all change considerably during development (Taylor et al. 2004). In addition, the homology between face-sensitive ERPs and ERFs is still unclear. As a result, objective methods are needed to assess the impact of maturation on face processing. One strength of the present study is that the beamforming/MSE/PLS approach is entirely data-driven. The beamformer weights were derived from the unaveraged single-trial sensor-level covariance structure. The MSE algorithm was applied to the single-trial source waveforms, yielding a dependent measure ($S_E$) that did not require any subjective judgment about peak morphology or latency. Statistical effects detected by PLS were computed as the (least-squares) optimal fit to the covariance between MSE and groups/conditions and are also data-driven.
4.4 Conclusion

Prima facie, brain activity appears unpredictable and noisy. However, it is becoming increasingly apparent that variability is not a trivial property of brain activity but a highly meaningful one. The interplay between local and global dynamics governs the spatiotemporal configuration of the brain’s functional architecture and keeps the system in a high-energy state, at the “edge of instability” among a number of different states and configurations (Ghosh et al. 2008; Deco et al. 2009). Intrinsic neural noise – stochastic fluctuations in information transfer due to imprecise timing of cellular processes – serves to nudge the system from one state to another and thus confers the capacity to make fluid and adaptive transitions between different states and reconfigure either spontaneously or in response to external (task) demand. This enhanced dynamic repertoire is expressed in the degree of variability of brain signals and reflects the contribution of both the nonlinear dynamics and noise of the underlying system.

We have demonstrated that brain signal variability is both task-dependent and regionally specific. Development was associated with more variable activity across the whole brain, but the most robust changes took place in the precuneus and posterior cingulate cortex. The face inversion effect was captured across ontogeny in the right fusiform gyrus. The fact that variability was modulated by task suggests a wide range of applications in cognitive neuroscience and we anticipate more effort in the future to establish the role of temporal predictability in the context of network structure and information flow. These data demonstrate that experimentally-induced deviations from regularity and predictability of neurophysiological brain signals are more than just a nuisance. They are an informative index that can elucidate significant developmental and cognitive effects, complementary to latency and amplitude measures of ERPs/ERFs as well as the power spectra of single trials.

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Figure 1: Source grid. Event-related beamforming (ERB) was used to estimate activity from 529 uniformly distributed sources.

Figure 2: Multiscale entropy (MSE). $S_E$ is plotted for the first 15 (coarse-grained) temporal scales $\tau$, from one representative source in the right fusiform gyrus. MSE curves were calculated for single-trial time series from which the subject- and condition-specific event-related field either was (b) or was not subtracted (a). Age group means are displayed separately. Error bars represent group standard errors.

Figure 3: Age effects captured by multiscale entropy (MSE). (a) Multivariate statistical contrasts (LVs) capturing the age-driven increase in MSE. (b) Maps of bootstrap ratios for each LV, showing brain regions at which the effect was statistically most reliable. The threshold is set at 12.3. Data are displayed separately for Inverted (left) and Upright (right) faces.

Figure 4: Age effect captured by power spectral density (PSD). (a) Multivariate statistical contrasts (LVs) capturing the age-driven increase in PSD. (b) Bootstrap ratios for each source (Fig. 1) and frequency band, not thresholded and corresponding to the effect immediately above. Warm colours indicate positive ratios. Data are displayed separately for Inverted (left) and Upright (right) faces. (c), (d): Maps of bootstrap ratios for two different frequencies for the LV associated with upright faces, showing diminished (1.25 Hz, c) and enhanced (13 Hz, d) densities. Maps are thresholded at a bootstrap ratio value of 10.5.

Figure 5: Inversion effect captured by multiscale entropy (MSE). (a) Multivariate statistical contrast capturing the difference between Upright (red) and Inverted (blue) runs, across age groups. (b) Statistical map of bootstrap ratios, showing brain regions that display the most statistically reliable differences in signal variability between Upright and Inverted faces across all age groups. Maps are thresholded at a bootstrap ratio value of 3.7.
Figure 6: Inversion effect captured by power spectral density (PSD). (a) Multivariate statistical contrast capturing the difference between Upright (red) and Inverted (blue) runs, across age groups. (b) Bootstrap ratios for each source (Fig. 1) and frequency band. Warm colours indicate positive ratios. (c) Maps of bootstrap ratios at 40 Hz for the LV shown in (a). Maps are thresholded at a bootstrap ratio value of 3.7.

Figure 7: Behavior and Behavior PLS Correlations for Inverted (blue) and Upright (red) conditions. (a) Group accuracy. (b) Group mean reaction time (RT). (c) Group coefficient of variation of reaction time (cvRT). (d) Correlations between MSE and age, accuracy, mean RT and cvRT. Error bars indicate group standard errors.