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Charting the maturation of the frontal lobe: An electrophysiological strategy

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Abstract

Tracking the functional development of specific regions of the prefrontal cortex in children using event-related potentials (ERPs) is challenging for both technical and conceptual reasons. In this paper we outline our strategy for studying frontal lobe development and present preliminary results from children aged 7–17 years and young adults using ERPs functionally associated with anterior cingulate and prefrontal cortex, especially the orbitofrontal, ventral, and medial portions. Our analysis of contingent negative variation, error-related negativity, and novelty P300 data show that the ERPs associated with these regions are still maturing into late adolescence, and that their amplitude has significant correlations with behavioral capacities.

1. Introduction

Neuropsychologists have known for a while that what are now called the executive functions associated with the prefrontal cortex are relatively late to mature, implying that the tissue itself continues to develop toward adult status well into adolescence (Kolb & Fantie, 1989; Stuss, 1992). However, this implication is not compelling since there could be other reasons for slow development of complex behaviors besides slow tissue maturation. More recently, there are emerging many reports of late structural development of the frontal lobes, from anatomical measures such as myelination, cortical thickness, dendritic, and synaptic proliferation to chemical characteristics (Benes, 2001; Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; Giedd et al., 1999; Huttenlocher & Dabholkar, 1997; Jernigan, Hesselink, Sowell, & Tallal, 1991; Lambe, Krimer, & Goldman-Rakic, 2000; Pfefferbaum et al., 1994; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Sampaio & Truwit, 2001). In addition, aberrations in this development are implicated in developmental clinical syndromes, such as ADHD and childhood onset schizophrenia (Gogtay, Giedd, & Rapoport, 2002; Tannock, 2003), and individual differences within the normal range also account for individual differences in behavioral development (Segalowitz, Unsal, & Dywan, 1992a). The link between frontal lobe structural development and behavioral sophistication has not been readily demonstrated in humans because of the paucity of noninvasive measures of frontal lobe maturation, although there is some such work with other primates (e.g., Raleigh et al., 1996). In principle, the development of functional brain imaging should be a great boost to documenting links between frontal lobe development and the child's growth in the mental skills we readily associate with prefrontal cortex (PFC). However, there are few studies comparing behavioral performances at various ages along with positron emission tomography (PET), function magnetic resonance imaging (fMRI) or electrophysiological measures. In this paper, we outline a strategy for charting the functional maturation of the prefrontal cortical regions in children and present some preliminary data using electrophysiological measures that can be readily related to PFC regions structurally and functionally.

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1.1. Relations among prefrontal regions: Distinct yet inseparable?

For our purposes here, we are interested in the PFC divisions of (a) the orbitofrontal (including a lateral inferior frontal portion and the temporal pole) and the ventral frontal region, (b) the dorsolateral PFC, and the (c) the medial frontal cortex, and in the functionally related anterior cingulate region. Excellent lesion work has attributed relatively different functions to each region. However, we also know that they interact heavily. The orbitofrontal cortex (OFC) has been linked to key mechanisms of reward, changes in reinforcement, extinction of behaviors no longer rewarded, and affect regulation (Rolls, 1998). The dorsolateral prefrontal cortex (DLPFC) is associated especially with working memory (Goldman-Rakic, 1987). The ventral and medial (VPFC and MPFC) and anterior cingulate regions seem critical for emotional regulation and the monitoring of performance for the purposes of self-regulation. Clearly there are linkages among the functions of the OFC, the VPFC and MPFC, and the anterior cingulate, and this is consistent with the fiber connections between the OFC and the cingulate cortex, and the fact that both have connections to the amygdala (Devinsky, Morrell, & Vogt, 1995; Rolls, 1998). This is also consistent with the increasing coordination among OFC, the ventral portions of the PFC and anterior cingulate cortex (ACC) regions during the maturation of extinction behavior in rats (Nair, Berndt, Barrett, & Gonzalez-Lima, 2001).

However, the OFC also has intimate functional relations with the DLPFC region. Both are important for the classic working memory task involved in delayed responding (Goldman-Rakic, 1987; Rolls, 1998). Furthermore, the assessment of executive function in children can be conceptualized as requiring an integration of the special functions of these two regions—working memory and inhibitory control. Some authors have suggested that challenges in clinical measures we associate with executive functions always involve both processes (Roberts & Pennington, 1996).

In addition, despite being designed for purely cognitive purposes, all executive function tasks can be seen as engaging an affective or motivational evaluation in normal children (Piaget, 1947), as well as some degree of inhibitory control and the avoidance of perseverative responding. Thus, standardized tasks probably activate multiple regions of the PFC. However, the contributions of each may be differentiable over time (i.e., one region may be more active than another at one time period following initiation of the trial) and for this reason the temporal resolution that is possible with electrophysiological technology is ideal.

The traditional approach to charting the development of executive functions has been to measure behavior at various ages, keeping the cognitive challenge constant. However, the danger in interpretation when using this method is that young children may use cognitive strategies different from those of older children and adults, and therefore different cortical tissue may be used to deal with the task (see Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002, for a contrast between child and adult regional activation patterns). The skills implemented to solve cognitive challenges may differ considerably in children compared to adults, and therefore what may seem like a reasonable measure of executive function associated with frontal tissue in adults may reflect skills associated with different brain regions in the child. The only way to verify the association between brain structure, function, and behavior is to have an online measure of tissue activation in the child that we can relate to their executive (or other) performance and compare this to adult behavior and brain activation. But this is difficult using current imaging techniques such as PET and fMRI because of both expense and ergonomics (remaining immobile within a confined space is often intimidating for children). In addition, it is difficult to examine specific aspects of information processing because of a lack of temporal resolution with these methods. Although fMRI can produce a time-locked "snapshot" of brain activation, it is not fully clear how accurate the time-locking is because of variance in the hemodynamic response, and there is no way to gather continuous activation figures in order to map out the peak value. Electrophysiological measures are able to avoid these limitations.

Our approach is to obtain an independent measure of regional activation of the frontal lobe using event-related potentials (ERPs), and then correlate these with development of known executive functions, and chart this relation through ontogenesis. If it is indeed the case that regional cortical activation in response to cognitive challenges can be reflected in ERPs, then we should see the presence of these ERPs correlated with cognitive behavioral development. This has been done in the developmental ERP literature many times (e.g., Howard & Polich, 1985; Segalowitz et al., 1992a; Stauder, Molenaar, & van der Molen, 1993), although most studies do not focus on the regional generator for the ERPs in question. What is needed is a data set from children of various ages on batteries of ERP and of cognitive behavioral measures. The ERP paradigms should be designed to tap into various cognitive information processing centers in the brain while not themselves being highly taxing of complex executive functions, and the behavioral measures should reflect both skills associated with executive functions and skills associated with simple cognitive (nonexecutive) functions. In this way, we can test the hypothesis that the development of behavioral executive functions are dependent on maturation of the cortical regions we associate with these functions without confounding the ERP output with the other variable of interest, i.e., executive function

performance. This research strategy requires that the two sets of measures be independent of each other to avoid obvious circular reasoning.

While the growth of executive function skills are more usually noted by their absence than their presence, the strategy outlined here moves somewhat in the more positive direction of showing the development of a relationship linking frontal lobe activation and age-related executive function performance. We present here some preliminary results from such a study. While we must collect more data to verify the patterns that are appearing, we are able to take some clear lessons from them concerning neuropsychological development, and are able at this point to draw (perhaps speculative) conclusions about maturation of the child's brain and the growth of behavioral and cognitive competence.

1.2. Features of event-related potentials

The electroencephalogram (EEG) is a measure of brain electrical activity measured from the scalp. The raw EEG represents the sum of extracellular current flow associated with dendritic excitatory and inhibitory postsynaptic potentials (rather than summed action potentials) of perhaps thousands if not millions of cortical connections (Pedley & Traub, 1990). Averaged ERPs are obtained by time-locking the EEG to a series of events (e.g., stimulus presentations or motor responses) and then averaging together these epochs. It is primarily this averaged ERP waveform that is scored and interpreted but sometimes single ERP trials will be used in analyses. Thus, ERPs are voltage changes generated within the brain that are associated with sensory, cognitive, or motor events and can be recorded from scalp electrodes (Regan, 1988). The ERP waveform provides information about the temporal aspects of information processing as well as its amplitude, which is measured in microvolts (μV) and can be positive or negative relative to a baseline EEG, usually taken as a brief period before the stimulus onset.

Different ERP waveforms are elicited by different types of events or activities, characterized by a series of components. These components can be thought of as being generated by one or more electrical sources, referred to as dipoles, that spread a positive voltage in one direction and a negative voltage in the other. We presume that these dipoles are physically located in cortical tissue, within cortical columns of neurons that have specialized functions and that act together. The waveform components elicited within a particular paradigm can often be associated with particular cognitive functions; for example, the common P3b is associated with the subject's evaluation of and allocation of attention to a salient stimulus (see Fig. 1). Components that are positive are labeled with a P and negative-going components are labeled with an N, followed by a number

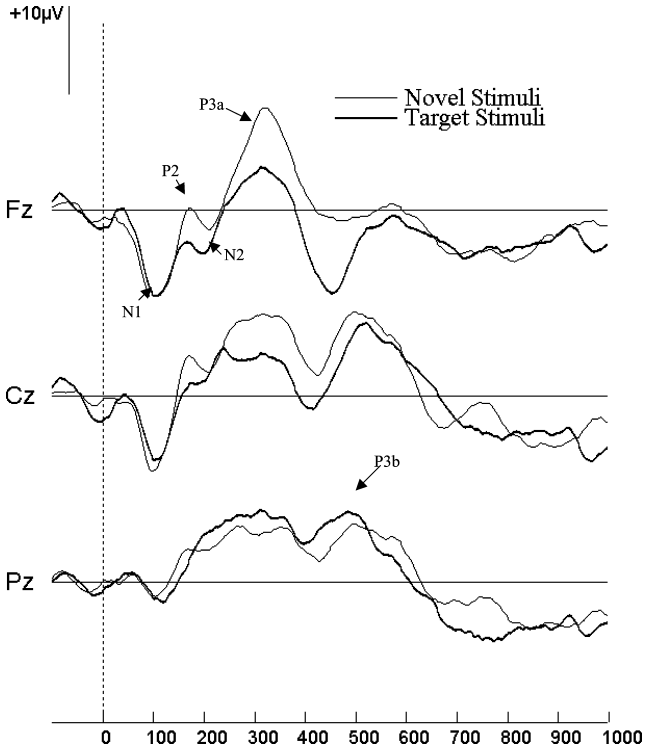

Fig. 1. Average for the adults in the oddball paradigm to novel and to target stimuli. The later P300 response (the P3b) has a much greater amplitude at the centroposterior sites compared with the frontal site, while the earlier P300 to the novel stimuli (the P3a) is primarily frontal.

indicating the latency in milliseconds from the time of the time-locking event (usually the stimulus) or a sequence number. Thus, the label P300 denotes a positive deflection that (in the original research describing it) occurs about 300 ms following the event of interest. Over time, some labels have come to designate a theoretical construct or an implied brain process. In this case, P300 (or sometimes shortened to P3 or P3b since by coincidence, it is the third major positive peak) is used to refer to a component that very often appears when attention is directed to a salient stimulus. N100 is shortened to N1 and P200 to P2 and N200 to N2 (see Fig. 1).

1.3. ERP mapping of the brain over age

While electrophysiological brain mapping of ERP change with age is theoretically possible, it has not been done in a systematic way for a variety of reasons, partly due to how recently the technology has evolved to allow quick application of electrodes and multi-channel recordings and analysis, and partly because there has been no accepted standard for many of the cognitive tasks of interest. With the advent of high density EEG montages came the capability of presenting scalp topographies of ERPs and EEG in much better detail than is possible with the classical few electrode placements (Duffy,

1986). With the very high densities now available (64, 128, or 256 electrodes), data reduction techniques such as Brain Electrical Source Analysis (BESA) can now model dipole generators that account for the particular ERP components of interest (Scherg & Berg, 1991). This permits us to take advantage of the rich experimental history concerning some ERP paradigms, and to eventually measure the contribution of generators in cortical structures specific to the ERP component under examination. For example, Hegerl and Frodl-Bauch (1997) report two dipole generators (one ventral and one dorsal in the temporal lobe) of the P300 whose amplitudes have higher retest reliability than does the original scalp-measured P300 amplitude. Another approach to this modelling showed that the dipole in the anterior cingulate of middle-aged adults shows reduced activation of this source compared to that in young adults (Ferrandez & Pouthas, 2001). Even small separations within PFC structures have been shown to be possible with high electrode densities (Luu, Tucker, Derryberry, Reed, & Poulsen, 2003). Thus, once we determine reliable age changes in ERP components that are associated with key structures in the prefrontal cortex and that can be related consistently to orbitofrontal and related circuitry, we will able to systematically analyze the amplitudes of particular generators as they activate and deactivate during a thinking task as a function of age and performance. This information can help clarify the contribution of specific brain regions for particular behavioral tasks and possibly lead to information about when these structures come 'online' for performing tasks in children and adolescents.

Our data here are the first instalment on a large study involving children from 7 to 17 years relating ERPs in cognitive paradigms that in adults reflect activation in the PFC regions. The electrophysiological measures reported here are components of ERPs based on three perceptual-attentive paradigms: the contingent negative variation, the novelty P300, and the error-related negativity. In all instances, younger children show specific reductions in the ERP components associated with PFC. The astonishing aspect of our data set is how late this immaturity in ERP morphology persists, continuing into very late adolescence. At least two of the paradigms have been associated with the cortical dopaminergic system, which would of course account for the late maturation of the ERPs and relate to the late maturation of executive functions associated with PFC (Diamond, 2001). However, in each case, the situation is considerably more complicated than simply a delay due to dopamine immaturity (Lambe et al., 2000).

1.4. The Contingent Negative Variation

The Contingent Negative Variation (CNV) was first introduced almost 40 years ago (Walter, Cooper, Aldridge, McCallum, & Winter, 1964) and is of interest because it is associated with activation in the prefrontal cortex (Basile, Brunder, Tarkka, & Papanicolaou, 1997; Fuster, 1987; Yamamoto, Saito, & Endo, 1986). The cognitive generator in adults is simple attentional anticipation: A first warning stimulus is a cue that a second stimulus is about to appear, to which the subject responds (usually by pressing a key). After the initial response to the warning stimulus is completed, a negativity develops up until the second stimulus appears. This negativity has been shown to relate to performance on psychometric measures associated with executive functions, and by extension to functional capacity of the PFC, in adolescents (Segalowitz et al., 1992a), adults with traumatic brain injury (Segalowitz, Unsal, & Dywan, 1992b), and older adults (Dywan, Segalowitz, & Williamson, 1994).

Several factors influence the amplitude of this negativity, including sleepiness (Coons, Murphy, & Segalowitz, 2002; Yamamoto, Saito, & Endo, 1984), motivation (Davies & Segalowitz, 2000; Irwin, Knott, & McAdam, 1966), and distraction (Tecce, 1979). In the study presented here we use a Go–Nogo paradigm, where the first stimulus not only warns of the impending second stimulus, but also indicates (by its color) whether or not the subject should respond to the second stimulus. In order to increase motivation and focussed attention during what is otherwise a fairly boring task, we present the task as a contest to the participants encouraging them to respond quickly in order to beat the best time of previous participants. The usual adult result is that the warning stimulus in both Go and Nogo trials produces a response (known as a P300 complex), with the Nogo waveform returning to baseline, and the Go waveform developing a negativity leading up to time of the second stimulus (see Fig. 2). Generators of the CNV are thought to vary with task and stimulus parameters, with sources reported in DLPFC, ventral and medial PFC, and basal ganglia (Bares & Rektor, 2001; Basile, Rogers, Bourbon, & Papanicolaou, 1994; Rosahl & Knight, 1995). The PFC matures through adolescence for this attentional function (Goldman & Alexander, 1977). Behavioral measures such as perseverative errors on the Wisconsin Card Sorting Test, mazes from the Wechsler Intelligence Scale for Children—Revised, 'g' intelligence tests such as the Culture-Fair Test, (Cattell & Cattell, 1960) associated with the frontal cortex have been shown to correlate with the initial portion of the CNV (the O-wave) in various human groups as would be predicted from this model (Dywan et al., 1994; Segalowitz et al., 1992a, 1992b). In addition, patients with severe head injury (who are at serious risk for PFC damage) either show no negativity or one that appears on both Go and Nogo trials, the latter situation hypothesized to be a result of OFC dysfunction (Campbell, Suffield, & Deacon, 1990). Similarly we might expect that the immature brain would show either no CNV negativity or an inability to inhibit

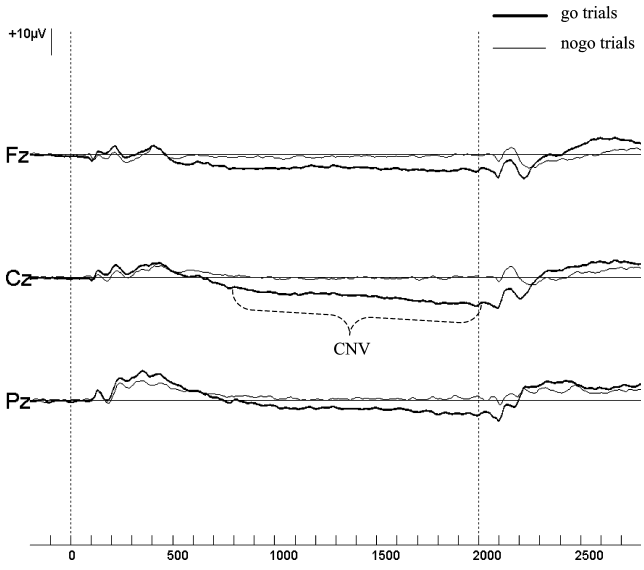

Fig. 2. Midline waveforms for the average of adults in the CNV paradigm, for the Go and the Nogo trials. The latency in milliseconds is marked along the X-axis, with the warning stimulus occurring at time 0 and the second stimulus onset is at 2000 ms.

it on Nogo trials. (Actually, the situation is more complicated because of a distinction between an early and late CNV component and the confounding of the later portion with movement potentials associated with the pressing the key. However, as will be come clear below, such distinctions did not appear in our data set and therefore we will not elaborate on them here.)

Preliminary analysis of our own data set confirm ventral PFC involvement in the adult CNV (see Fig. 3). A three dipole model accounted for 94% of the variance in the ERP from 900 to 1900 ms after stimulus onset, with a right ventral source (appearing to be in the BA 11 region) accounting for 54% of the variance on its own, a medial source in the M1/S1 region accounting for 45% of the variance on its own, and a left ventral temporal pole (BA 30) source accounting for 8% on its own but focussing its effect on the midline negativity of the CNV. When we examine the model at about 1000 ms before the second stimulus (during the early orienting component of the CNV), the OFC source accounts for 66% of the variance alone and together with the medial source accounts for 92%. Of course, such a model must be preliminary because we have only 29 electrode sites, with none below the level of the scalp; further work will be needed to confirm this OFC involvement. Nevertheless, this strategy should allow us to focus appropriately on the development of these components in children.

1.4.1. Previous studies relating to CNV in childhood

The previous literature is primarily characterized by its paucity and inconsistency. Cohen, Offner, and Palmer (1967) briefly reported that the CNV continues maturing into the third decade after birth, with less anterior–posterior differentiation in younger children. Since then the few reports on children's CNVs generally indicate that they are poor, and even reversed in 6-year-olds in the movement potential paradigm (Warren & Karrer, 1984) and in a standard CNV (Austin, Berg, & Fields, 1996). In contrast, in a study comparing the CNVs of children with medically treated headache, control children 8- to 14-years old ($M = 11$ years) produced a healthy early and late CNV but these did not differ across the Go and Nogo trials (Sartory, Besken, & Pothmann, 1997). There are other various reports of successful eliciting of CNV in adolescents or even young children if one removes the requirement to sustain attention in the absence of an overt stimulus (Prevec, Ribaric, & Butinar, 1984), but these studies generally do not report changes over age. The only exception is a report that the CNV steadily grows from an absence at age 6 to full adult level at age 11 years (Timsit-Berthier & Hausman, 1972). In contrast to this finding, however, we found earlier that the CNV was still not at adult levels by age 12 years, and was intermediate for 12-year-olds with high IQ (Segalowitz et al., 1992a). Thus, while there are relatively few studies on the CNV in children, and some disagreement as to the developmental course, there is consensus that it relates to activation of the frontal attention system, and has the potential to index the growth of this system as it functions in the PFC.

1.4.2. CNV development in children across adolescence

We have examined so far the CNV in 57 children (7–17 years) and 20 young adults (19–25 years) in a standard CNV paradigm with 2 s stimulus onset asynchrony (SOA) between stimuli (40 Go and 40 Nogo trials) and a variable intertrial interval (4–7 s), with bandpass of .03–100 Hz, referenced offline to an average of the two ears. The warning stimulus was either a green (Go trials) or red (Nogo trials) circle, with the imperative stimulus being a graphic of a racing car. Thus, the warning stimulus served as the Go–Nogo indicator. Average amplitude was measured in several epochs (400–800, 800–1200, 1200–1600, 1600–2000, and the 800–2000 ms following the warning stimulus onset). Age correlated significantly with CNV amplitude for all epochs at Cz for Go trials (.49, −.54, −.34, −.41, −.46, $p < .002$ for the 5 epochs) and somewhat less so or not at all at Fz and Pz. The Nogo trials do not correlate with age for any of the epochs or sites. Thus, the negativity of the Go trials increases with age but children's EEG is similar to adults on the Nogo trials (see Fig. 4). Response times correlated with age in Go trials ($r = -.63, p < .0005$) with adults generally responding faster than young children. The children and adults had similar accuracy on this CNV task i.e., there was not a significant difference between age groups in the mean percent correct responses on Go trials, $F(10, 66) = 1.08$, n.s. The means

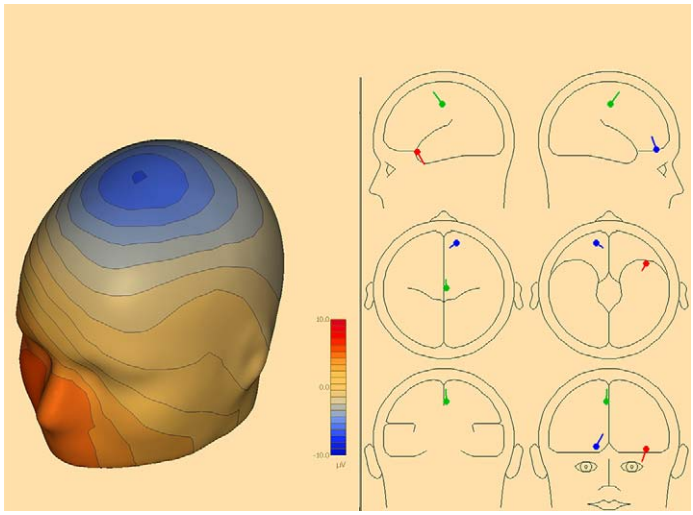

Fig. 3. Left: The scalp topography of the adult CNV to the Go trials showing a clear central maximum. The 3-dipole solution in BESA accounts for 94% of the pattern with most of this in orbitofrontal and temporal pole generators.

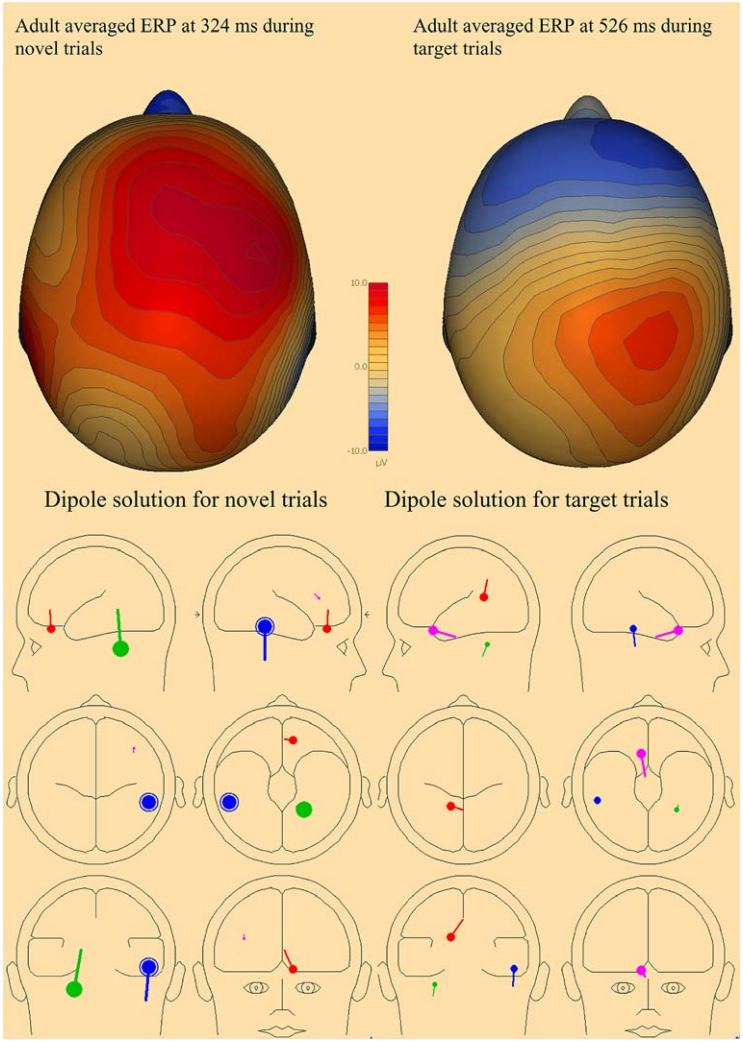

Fig. 6. Top: Scalp topographies for the P3a during novel stimulus trials and the P3b during target stimulus trials. Bottom: The BESA dipole solution includes an orbitofrontal generator for the novel stimulus trials and a medial temporal generator for the target stimulus trials.

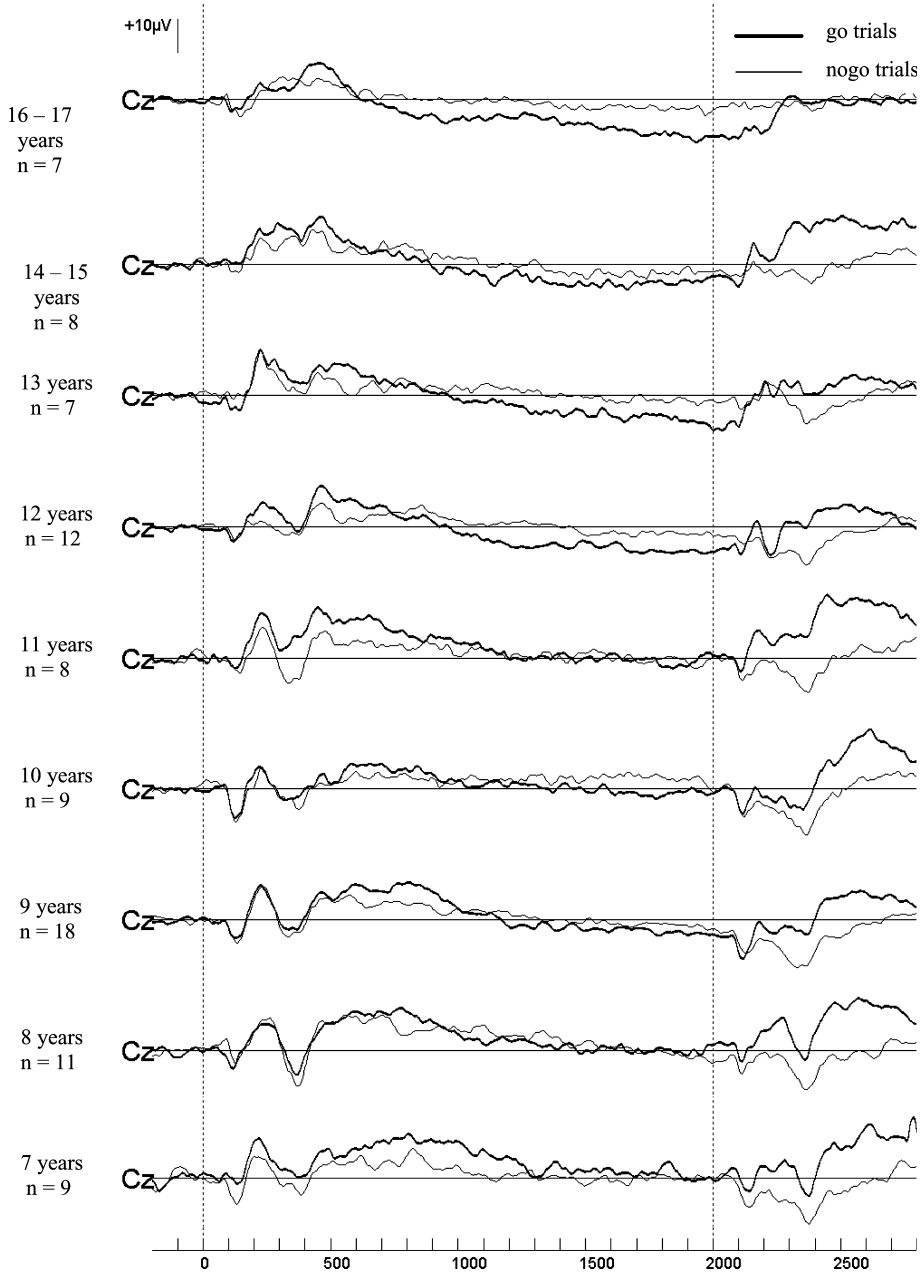

Fig. 4. Averages of the CNV for Go and Nogo trials for each age grouping. The response to the Nogo trials does not change over age while the CNV to the Go trials shows considerable development through adolescence.

ranged from 76 to 96% with the 7-year-olds having the highest score and adults having 86% correct. Only 15% of the participants responded on Nogo trials (2 adult and 4 adolescents and 5 younger children responded on 1 or 2 Nogo trials); all other participants made no errors on Nogo trials (false alarms).

While space does not permit a full rendition of how the CNV amplitudes correlated with behavioral performance on a variety of tasks designed to challenge executive functions versus nonexecutive functions, there were significant correlations between CNV (with the variance accounted for by age removed) and working memory (2-back), word recall, Stroop interference, vocabulary, and some measures of perceptual-motor speed, but no evidence of correlation with measures of simple attention (Digit Span) or perception (Line Orientation). Stronger effects are found when the correlations are restricted to subjects in the younger age ranges. This suggests that there are factors other than age influencing CNV amplitude in preadolescents and adolescents, which accounts for some of the residual variance in the correlation between age and CNV amplitude, i.e., there are individual differences in CNV within ages due to other, presumably cognitive, factors.

Of special interest was the qualitatively different pattern shown by the younger children. The adults virtually always showed the expected difference between Go and Nogo trials, with the negativity greater on the Go trials, replicating earlier studies. The older children mostly showed this mature pattern while the younger children did not. In fact, the youngest children showed a frank reversal of the Go–Nogo effect, with the Go trials producing a prolonged positivity (replicating Warren & Karrer, 1984, see Fig. 5 for some such examples). This reversal gradually subsided with the older children until the adult pattern was achieved. These results differ from those of Sartory et al. (1997) who found that 11-year-olds showed CNV-like negativities for both Go and Nogo trials, suggesting a hypervigilance in that group. Our data, in contrast, suggest an age-related qualitative change in the organization of the frontal attention system. However, some children despite their youth do produce a negativity on CNV Go trials, similar to those of adults, and it will be interesting to see whether these children show especially good maturation on executive functions associated with dorsolateral and orbitofrontal cortex.

The qualitatively different pattern shown by the younger children in our CNV data might also be explained by the fact that the inherent characteristics of child ERPs might be masking the expected effects. As shown in Figs. 2 and 4, the positive (i.e., P3) component following the first stimulus returns to baseline around 500–700 ms for adults and older teenagers, but in the young children it does not return to baseline until at least 1000 ms. This extended positive component in young children could be obscuring the negative component (i.e., CNV) leading up to the second stimulus. Further research is needed to address this issue.

Our results lead to several important conclusions. First, they show functional evidence, more direct than behavioral measures, that the frontal lobe is continuing to develop in major ways right through adolescence. Second, they suggest that there are cognitive and behavioral skills associated with CNV amplitude (and presumably the frontal lobe generators) in preadolescents and adolescents within age groups, suggesting that a major component to intellectual development in adolescents is the maturation of the frontal lobe attentional system. Third, they suggest that younger children can sustain attention (since they complete the task well based on the accuracy and false hits data) but use mechanisms that are different from those of adults. Fourth, the results corroborate considerable discussion

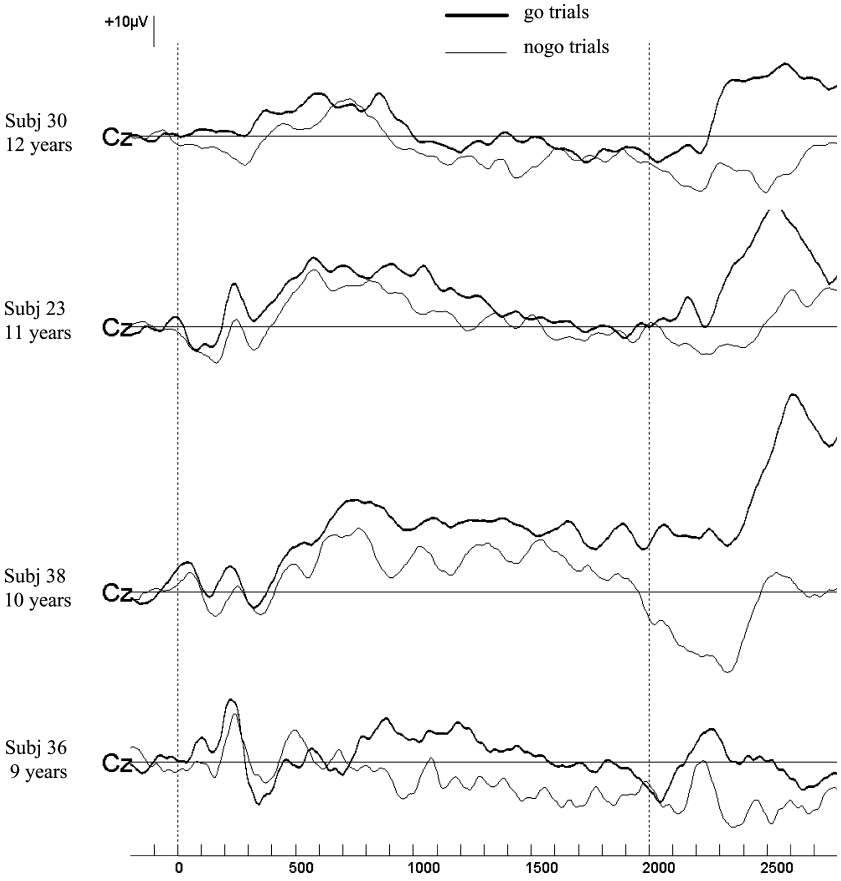

Fig. 5. Some examples of adolescents whose waveforms to the Go trials indicate a positive instead of the usual negative CNV waveform.

of late that the frontal lobes may take a much longer time to mature than was traditionally thought, with even youth in the middle teen years not reaching the brain activation pattern of adults on this very simple, easily accomplished task. As we shall see, this conclusion is consistent with other ERP paradigms.

1.5. P300 family of components

The P300 is produced when one attends to a stimulus, and is often interpreted as the first major component reflecting controlled attention to the stimulus. The traditional paradigm (and its variants) presents a series of stimuli at intervals of at least 1 s, some of which may require more attention and/or response than others and are usually more infrequently presented than other nontarget stimuli in paradigm. This produces a relatively consistent and large positivity 300 to 500 ms after the stimulus onset. The ease of obtaining and scoring the P300 has promoted its use in well over 1000 studies in the last 25 years. In such a standard paradigm, it has as good test–retest reliability as many cognitive measures used in research, although not as high as clinical measures that have been honed expressly for that purpose (Segalowitz & Barnes, 1993). The most obvious developmental changes involve a speeding up of the P300 peak from childhood to late adolescence, a levelling off in young adulthood, and then a gradual increase in latency with adult aging (Pearce, Crowell, Tokioka, & Pacheco, 1989; Polich, Howard, & Starr, 1985). Along with adult aging also comes a reduction in P300 amplitude. However, the reverse is not so clearly the case in adolescent development. Some authors report a larger P300 amplitude in childhood reducing to the adult level by adolescence (e.g., Berman, Friedman, & Cramer, 1990; Stauder, Molenaar, & Van der Molen, 1999), while others report a smaller P300 amplitude (e.g., Segalowitz et al., 1992a), and yet others report no change over age (e.g., Johnstone, Barry, Anderson, & Coyle, 1996). Few of these studies span the full age period from early childhood to adulthood, despite one of the benefits of the P300 measure being that its standard procedure can be administered equally to children, adults and, for that matter, participants with brain injury. Further complicating this scenario is that the P300 can vary across paradigms, and therefore possibly across age if age-related changes in waveform morphology mimic to some extent the differences across paradigms. This can happen (at least in theory) if the task demands are such that they elicit considerably different processing strategies in those individuals for whom the task is more of a challenge. For example, the simplest paradigm is to present a series of stimuli. When visual stimuli are presented in this way to infants, the youngest (1–6 months) show large components earlier than the P300 (N1 and P2, which are usually associated in adults with relatively automatic processing not dependent on conscious strategies) but virtually no P300, suggesting that infants demonstrate immediate stimulus processing only (Vaughan & Kurtzberg, 1992). The dramatic development of the P300 in children suggests a deeper processing of the stimulus, perhaps due to the exuberant growth of dendrites and synapses during this period.

The further complication mentioned earlier reflects that there are multiple generators to the P300, some distant enough that we can talk about two relatively distinct P300 components, the P3a and P3b. The P3a appears to reflect an initial orienting to the stimulus that is fast but does not reflect deep processing. This peak can occur quite early, sometimes before 300 ms after the stimulus onset, and the physiological generator appears to be in the PFC. It is quite evenly distributed across midline scalp sites, often with a maximum at the frontal site Fz, in comparison to the P3b whose maximum is clearly more posterior, usually at the Pz site. Lesions and anatomical studies have verified this frontal–posterior distinction for the two P300 types (Ford et al., 1994; Knight, 1984; Verleger, Heide, Butt, & Kompf, 1994). If the P3a reflects an initial orienting to the stimulus and the P3b reflects a deeper processing of the attentional demands, then the P3a component should be more prominent when the stimuli (or task) are new to the subject. This is exactly what happens in the novelty paradigm, where besides presenting rare target and frequent nontarget stimuli, stimuli that are presented only once (and therefore are novel) also appear. Despite not demanding a response, these stimuli elicit a large P300 that tends to be frontally maximal. Further, in the initial stages of the test period, even the repeated target stimuli are relatively novel, compared to how they will feel to the subject after several dozen presentations, and so they should also produce a larger P3 at Fz than they will on the later trials (Segalowitz, Wintink, & Cudmore, 2001).

A complicating factor is that when the processing becomes more challenging for the subject, the P3a and P3b will separate because the initial orienting to the stimulus will be followed by a deeper attentional processing that will be reflected later in the ERP because it takes more time (Kok, 2001). This happens a great deal with memory studies, where the later P3b becomes so drawn out that it is referred to as a 'late positive component' (e.g., Dywan, Segalowitz, & Arsenault, 2002). This raises another concern with developmental studies. If the P3b appears to be different from that in adults, is it because the task is more demanding for children and what we think of as their P3b is really their P3a, i.e., it appears later at about the same latency as the P3b would appear (since the P3a is earlier than the P3b but children's P300 latencies are longer in general), and is more frontally based than in adults? If this is the case, the

children's 'real' P3b would be more like a late positive component and more difficult to identify as a P300 component. For example, Stauder et al. (1999) reported a dramatic drop in late positivity in 5- to 7-year-olds. Clearly this problem depends on the particular paradigm presented, and each study must be evaluated individually with respect to this.

1.5.1. P3a and P3b across adolescence

Our research paradigm was to maximize the likelihood of measuring P3a and P3b, while minimizing the possible confounds outlined above. The compromise we adopted was a simple auditory discrimination task requiring the child to press a key when a high-pitched tone was played (11% of trials), and to not press otherwise. We also presented novel sounds (11% of trials) of equal duration but which were very perceptually salient—a tone gliding over a span of 300 Hz. We found in an earlier study that these gliding tones produced a clear and powerful P3a (Segalowitz, Bernstein, & Lawson, 2001).

The adult subjects in our study produced both early and late components, with the amplitude of the earlier one more frontal on the novel trials and the later one having a larger amplitude posteriorly (see Fig. 1). While there was some variability in the adults, in general they showed this pattern of a frontal maximum in response to novel stimuli (i.e., primarily reflecting the P3a) with a positivity that was still quite large in the more posterior scalp region, and a posterior maximum in response to targets (i.e., the P3b) with a steep gradient blending into a negativity frontally. When a preliminary source analysis is applied to the group's average ERP of the novel trials' using BESA 2000, 4 dipole sources account for 91% of the variance at 324 ms (where the Fz positivity is maximal). Two dipoles are clearly contributing to the positivities at the midline, one in ventral OFC and the other in the ventral temporal region. The limitation of only 29 EEG sites with none below the scalp line limits the reliability of the solution, but it nevertheless suggests an OFC component for the frontal aspect of the positivity. The later target P3 (i.e., the P3b at 526 ms) producing the centroparietal positivity derived no frontal generators at all, but rather one that is placed in the medial temporal lobe (see Fig. 6). Source analyses on the individuals will have to be done to verify the consistency of this pattern.

Preliminary analyses of the data from the children in our study supported the pattern we expected from the literature. The younger children produced large P300s in the target trials with a posterior maximum, but very unclear and inconsistent results for the P300s to novel stimuli. It was really only by age 13 that the children started to show the standard adult pattern. We are in the very initial stages of analysing the P300 data in this study and thus we will not report behavioral data or correlations with other cognitive tasks.

1.6. Error monitoring and the error-related negativity (ERN or Ne)

It was recently discovered that when someone realizes they are about to make an error or have made one, there is a negative component generated in the frontocentral region, probably in the anterior cingulate region, which has intimate interactions with OFC circuits as mentioned earlier. It went undetected for many years because normally one averages ERP trials time-locked to the stimulus onset. However, this internal response (feeling whatever one feels when a performance slip is in production) is more closely tied to the response time and usually peaks at about 150 ms following response onset (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991). After all, if the person realizes that a performance slip is about to be committed, and he or she has enough warning, then it will be corrected. This realization must come after the "point of no return" (150–200 ms before the key is actually pressed), and thus the response is a better indicator than is the stimulus onset of the timing of this realization. The typical task used is a simple perceptual discrimination where the task is to press a key with the left index finger for one letter, and with the right index finger for another. Traditionally, these are flanked by letters conflicting with the central target on some trials, causing more difficulty and a reasonable error rate of around 10%. While this Eriksen Flanker task (Eriksen & Eriksen, 1974) has been used to produce the error negativity very often, more complex processing will also produce ERNs (Dehaene, Posner, & Tucker, 1994; Mathewson, Dywan, & Segalowitz, 2002). It is generally accepted that the source is in the anterior cingulate, especially the ventral portion (Dehaene et al., 1994; Stemmer, Segalowitz, Witzke, & Schönle, 2003) and dipoles are placed there regularly by source analyses (e.g., Luu et al., 2003; Van Veen & Carter, 2002).

That the anterior cingulate cortex (ACC) should house the generator for an error-related component makes sense from a variety of perspectives. The ACC is particularly activated by tasks that produce response conflict (e.g., the Stroop task, or stimulus–response incompatibility tasks) as shown on PET and fMRI studies (see Botvinick, Braver, Barch, Carter, & Cohen, 2001, for a review). However, in all these tasks there are multiple mental events happening around the same time (i.e., response, cognitive, and emotional conflict responses). When a simple slip (not an honest mistake which one does not try to correct) is being made, one may engage a corrective movement, resulting in a response conflict of some sort. But one also senses a conflict between the response initiated and the response now desired (error detection), resulting in a cognitive

conflict response. Also, one feels somewhat chagrined by the slip about to be made, producing an emotional conflict response. Considering that the ACC region is involved in movement, cognition and emotional monitoring, and that the ACC has major connections to the basal ganglia, the dorsolateral prefrontal cortex, the orbitofrontal cortex and the limbic system, its centrality in all these functions is not surprising. There is evidence to suggest, however, that the ERN may relate more to the evaluative emotional and cognitive processes than to the response conflict per se. For example, a similar (or perhaps identical) electrocortical component is generated even when no response is being made (a medial–frontal negativity) in response to feedback from the trial, even feedback in a game that indicates that the best possible response was made although the outcome still means losing points (Gehring & Willoughby, 2002; Holroyd & Coles, 2002; Miltner, Braun, & Coles, 1997). In addition, trials that are responded to correctly, but on which one experiences a response conflict because of stimulus incompatibility factors, do not produce an ERN at all (Pailing, Segalowitz, & Davies, 2000). Also, the ERN amplitude has been linked to a number of personality traits that reflect worrying and caring about making errors rather than motor or cognitive factors (socialization: Dikman & Allen, 2000; OCD: Gehring, Himle, & Nisenson, 2000; impulsivity: Pailing, Segalowitz, Dywan, & Davies, 2002). Also, the ERN is attenuated when a low dose of alcohol reduces corrective actions following errors (Ridderinkhof et al., 2002). Thus, the ERN component probably reflects a late evaluative function (which could be emotional or cognitive or both) rather than an early information processing function such as response conflict.

1.6.1. ERNs across adolescence

We have examined the ERN data of 93 children (ages 7–17 years) and 27 adults (19–25 years) using the Eriksen Flanker task described above. As expected, there were age-group differences in response time with strong zero-order correlations between age and correct ($r = -.74$, $p < .001$) and error ($r = -.60$, $p < .001$) RTs, with asymptotes around 12–13 years. Consistent with previous findings, subjects were faster on error trials ($M = 399$ ms) than correct trials ($M = 491$ ms), $F_{(1,109)} = 308.8$, $p < .0005$. This was true for all age groups, suggesting that the children perform similarly on this task to adults. The mean RT for correct trials following error trials ($M = 527$ s) was significantly longer than the mean RT for correct trials following correct trials ($M = 488$ ms), ($F_{(1,109)} = 56.97$, $p < .0005$). This was true for each age group and the interaction between trial type and age group was not significant. Therefore, even the youngest children slowed on responses immediately following an incorrect response. Error rates ranged from 2.5 to 29.3% across subjects ($M = 11.5\%$). Error rates were similar for children and adults as there was not a significant difference in the error rates across age groups, $F_{(10,109)} = 1.33$, $p < .22$.

The adult subjects produced standard ERNs with great regularity, as is usually found (see Fig. 7). Correlation analysis revealed a general trend for the ERN amplitude to become more negative with age, $r = -.47, p < .0005$ with the young children not always

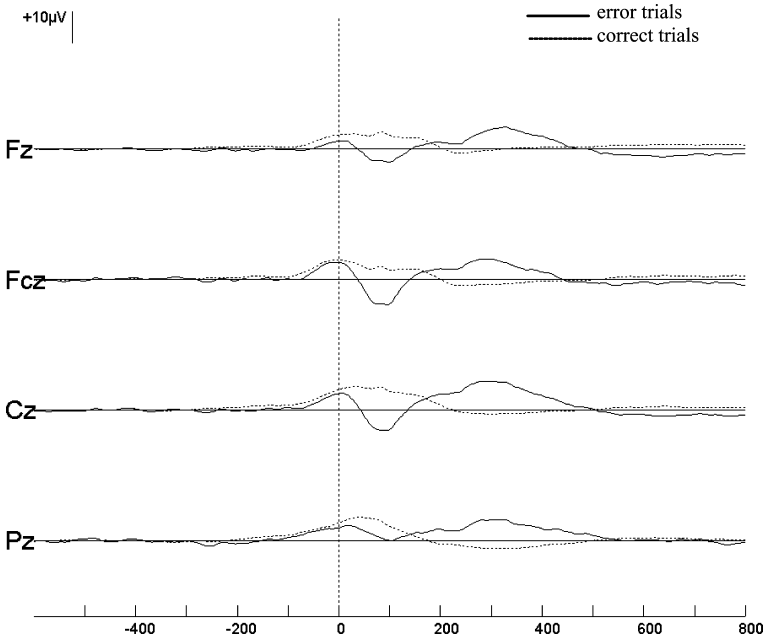

Fig. 7. Average of adults' waveforms time-locked to responses in the flanker task, showing the error-related negativity maximal at the FCz site. Latency along the X-axis is in milliseconds.

showing a negative component following the response. Considering that children do not like to make errors, we expected to find that they would produce easily identifiable ERNs. All three mechanisms hypothesized to underlie the ERN (response, cognitive and emotional conflict resolution) are experienced by children and indeed many children's games are based on perceptual discrimination and the making of rapid responses. However, as can be seen in Fig. 8, younger children in general did not produce waveforms even approximating those of adults, and even by middle teens, the waveforms had not reached those of young adults. There were, however, intriguing exceptions. Even amongst the 9-year-olds, the occasional child did produce a very clear ERN (see Subject 103 in Fig. 9).

For those children who show remarkably small ERNs, despite their obvious realization when they are making errors, it may be that they are not reacting to their slips in the same way as adults. Furthermore, it may be that reacting less is a positive strategy for learning, and may aid in some contexts. For example, when learning is in a social setting, such as when learning a second language, it is better to not worry about errors and slips and to continue trying to

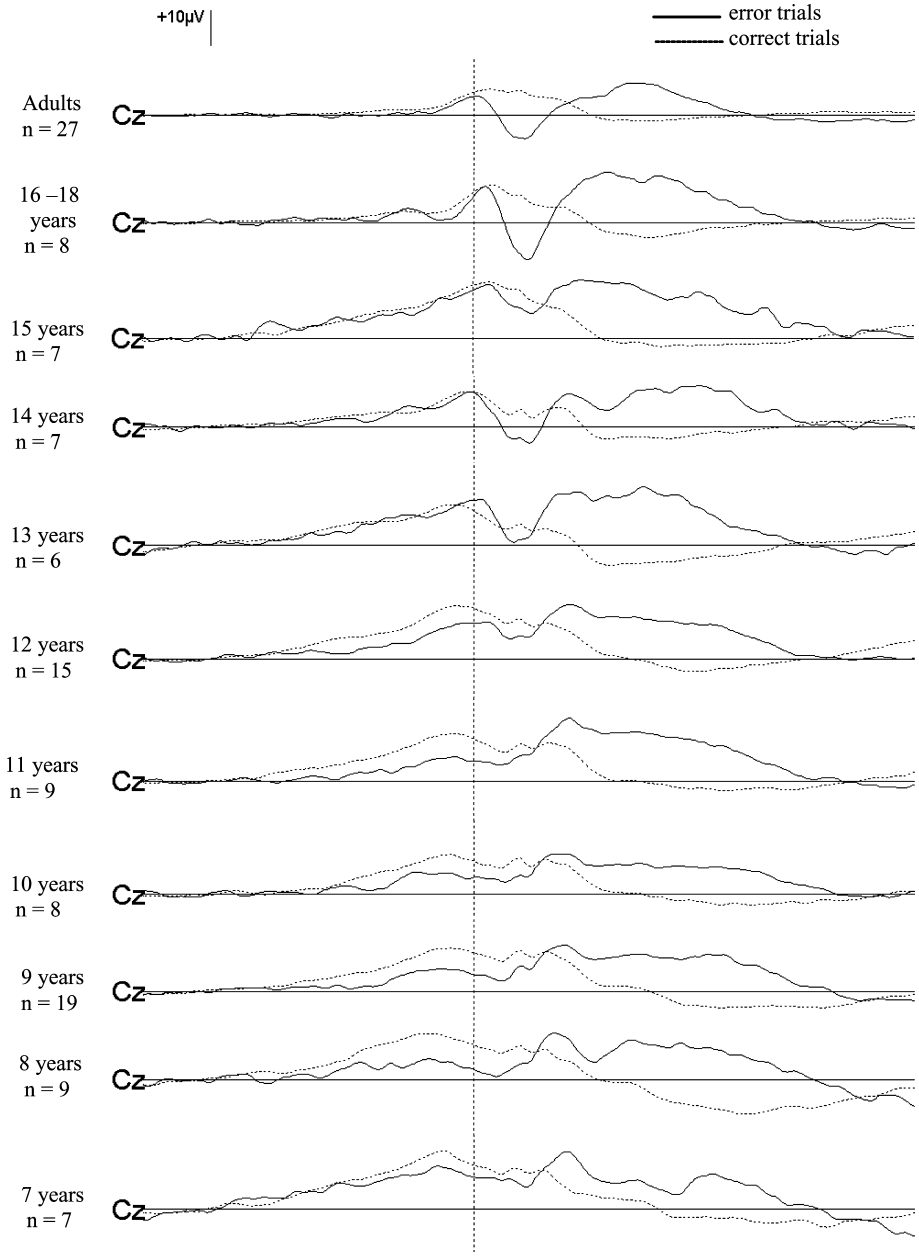

Fig. 8. Averages for each age group at Cz for the correct and incorrect responses in the flanker task, showing the development of the error-related negativity through adolescence. Latency along the *X*-axis is in milliseconds.

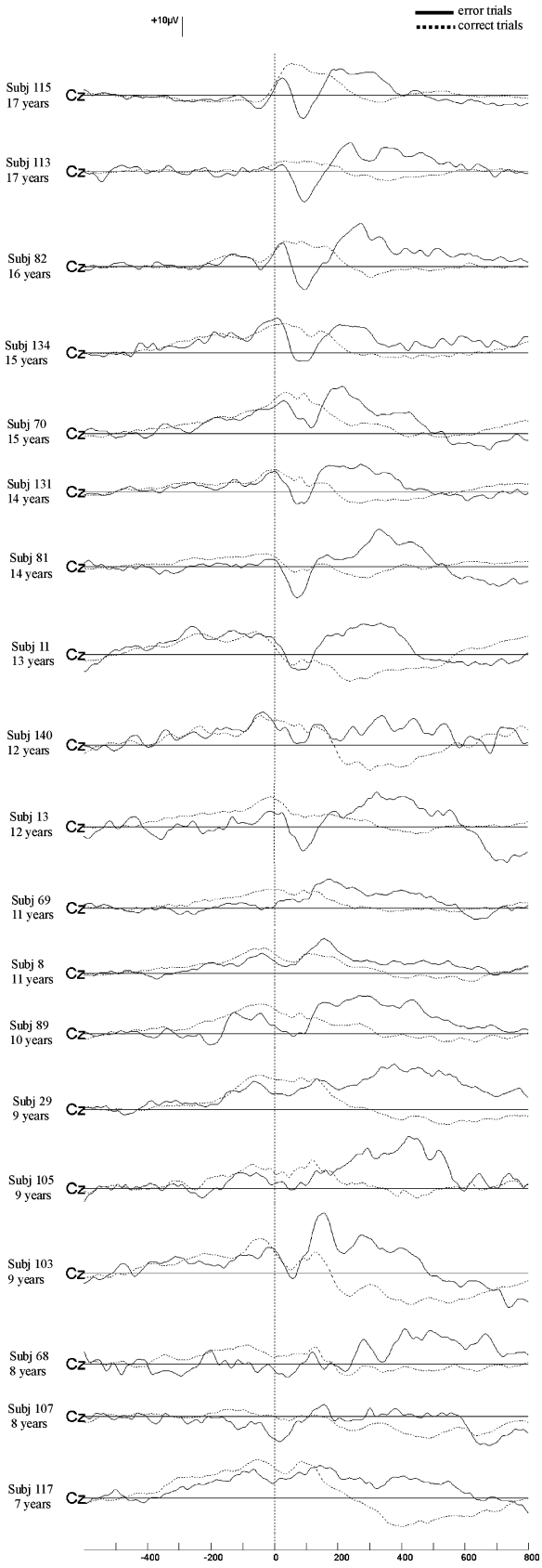

Fig. 9. Examples of children's waveforms, for correct and incorrect trials on the flanker task, with scorable ERNs. Latency along the *X*-axis is in milliseconds.

communicate. Much of children's learning might be in this mode, and adolescence marks a new sense of self-consciousness that makes such a strategy less feasible (Elkind, 1967). The development of ERNs may reflect the maturation of the ACC and a change in this factor.

Of particular interest are the few children who do produce a standard ERN waveform. Are these children more sensitive to their slips, or to the task demands? Or perhaps these children are activating frontal lobe tissue more than their peers, reflecting more mature ERN components like the adults. One might speculate that these children are more likely to be able to engage adaptive functions associated with the prefrontal cortex, perhaps associated with social resilience (i.e., being able to adapt socially in difficult situations because their self-monitoring is superior).

Further study is needed to determine the stability of these individual differences. While there are no reported data on the test–retest reliability of the ERN, the reliability of other ERP components have been documented at a level equivalent to many cognitive psychological measures, as was mentioned above (Fallgattera et al., 2001; Hegerl & Frodl-Bauch, 1997; Segalowitz & Barnes, 1993; Wolhovd & Fjell, 2002). By way of adecdote, we did notice, however, that the error-related waveform was more highly similar for a pair of 11-year-old identical twins (raised together) than across unrelated 11-year-olds (see Fig. 10).

2. Conclusions

A consistent theme in this preliminary data analysis is the heterogeneity of development in ERPs, which appears to be far greater than that indicated by simpler measures of information processing such as speed of processing (Kail, 1991). Although there have been no direct comparisons made, speed of processing also seems to correlate much better with age than do more complex measures associated with executive functions (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Klenberg, Korkman, & Lahti-Nuuttila, 2001) giving the impression that speed is the most stable facet of mental development and therefore the one underlying the others. Of course, this logic is not compelling. (Height and weight also progress systematically with age but can hardly be said to be the basic mechanism of psychological maturation.) Rather, we see the dynamic activation of specific brain regions as dependent on a number of factors leading to their heterogeneity, factors such as stimulus presentation parameters, the degree of the subject's engagement in the task, and, of course, cognitive and neuropsychological maturation. We expect considerable synaptic, dendritic, and neuronal change through adolescence (Gogtay et al., 2002; Huttenlocher & Dabholkar, 1997), which should be reflected

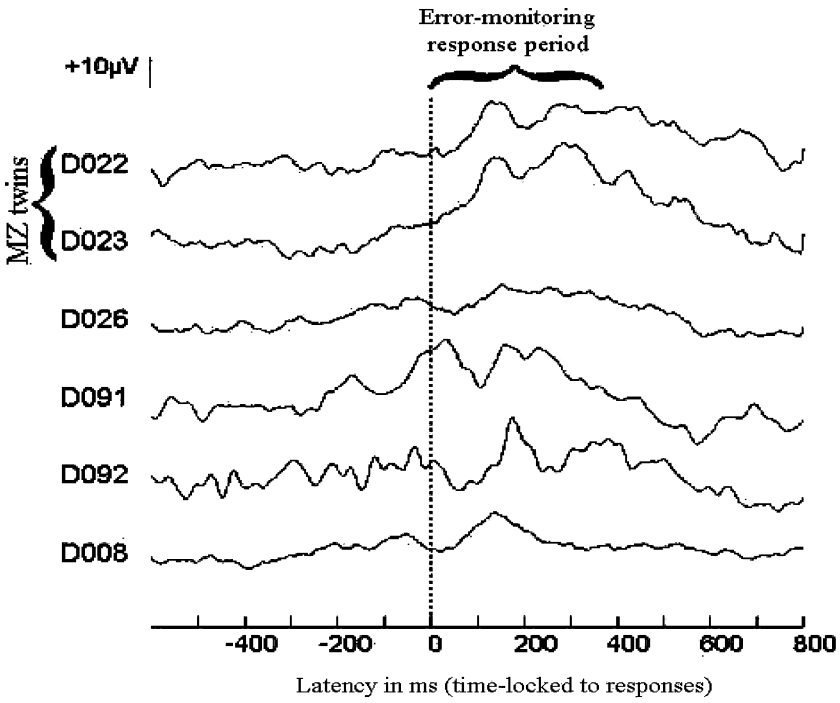

Fig. 10. Waveforms at Cz for error trials on the flanker task amongst 11-year-old girls. Subjects D022 and D023 are MZ twins who have remarkably similar components during the error-monitoring response period.

in cortical activation and regional interconnection measures. Hopefully these activation measures will reflect underlying specifics of brain growth in a way that is not confounded with the behavioral measures we are trying to account for.

2.1. Some technical issues

2.1.1. Brain size changes with growth

There are various factors that could account for immature ERP waveforms in children that in fact reflect differences between children and adults other than cortical maturation. The ERP waveforms we record at the scalp are reflections, after all, of the dipole generators within the brain. If brain growth in the child alters the orientation of these dipoles by changing the cortical folding, then the scalp ERP pattern will be considerably different. However, if the orientation angle of the dipole producing the ERN, for example, is different in children but still functional, then we should pick up the negativity at a different spot. For this, we need to examine the waveforms more carefully around the entire scalp, something which has not yet been done. However, we think increases in brain size to be unlikely as a source of ERP changes because the 7-year-old child's brain has reached about 90% of adult size (with full size by about age 11 years), and we do not think that the dipoles could shift so greatly given this maturational figure (Dekaban, 1978). While there are significant changes in grey and white matter during adolescence, which clearly can have major effects on cognitive functions (De Bellis et al., 2001), we doubt that the folding pattern of the cortex would alter with these changes, although this has yet to be addressed directly.

2.1.2. Signal-to-noise ratio

It could also be that the signal-to-noise ratio (SNR) of the electrical signal in children is much lower than that in adults, which would make ERP waveforms messier. For example, this could be a product of inconsistent timing of perceptual processes or of response initiation. While this needs to be checked with each data set, it is not likely to account for the changes over age because children are capable of producing reasonable N1 and P3b waveforms, so a lower SNR could not be a general property of the child's brain. However, this can certainly be a problem for some components, such as the ERN, that are time-locked to responses. Children's response times are longer than those of adults and have a larger standard deviation, as would be expected. However, the comparisons of ERP waveforms are on an additive model, and are not normally scaled in a multiplicative fashion. This is something that may need investigation in the future.

2.1.3. Cognitive strategies

Of more seriousness would be a concern that children do not treat even the simplest task with the same cognitive strategy as adults because they interpret the tasks differently. Detecting an alteration in strategy is of

course difficult. It is important to compare error rates, response times, and response variability across age groups, assuming that if the performance is reasonably similar across age, then we can conclude that they have similar goals at least. But we are left with a bit of a conundrum: While we design the task so that we have comparable cognitive processes across the age groups, we also would conclude that if the brain regions activated by a task are different in children compared to adults, then they must be utilizing different information processing strategies in some way reflected by the different brain activation. This follows from a basic premise of developmental neuropsychology that with growth, neurocognitive capacities change, which necessarily leads to different strategies for information processing. With respect to the paradigms presented here, we would expect that even for the simple tasks used, children and adults may exhibit different brain activation patterns because adults have access to a highly integrated prefrontal cortex and those networks are not mature in young children. Thus, children must rely on cortical networks available from other brain regions to perform the task. While ERP data cannot tell us which cognitive strategies are used by children compared with adults on a particular task, they can show that brain activation patterns are different in children in response to the same challenges. The research irony is that we need to have the children attempting the same strategy as the adults in order to make a fair comparison ofbrain activation patterns, and when we find that the patterns are different, we conclude that the information processing strategies must have been different. This situation holds of course for all brain imaging techniques, not just ERPs. For this reason, as indicated earlier, we would want to utilize a task with as simple cognitive demands as possible attempting to keep the cognitive challenge similar across age groups and the likelihood of adopting the same strategy as high as possible. While this issue merits further discussion, finding age effects in cortical activation patterns on such a simple task demonstrates to some extent the differences in cortical capacities and networks between children and adults.

2.1.4. Implications for understanding adolescent development

A principal issue concerns when major cognitive development stops. If the brain shows major changes through to young adulthood, it is hard to argue that the intellectual structures are all in place by, say, age 14 years, with only learning and experience left to take care of. Maturation of the brain's integrative units, especially those integrating affective responses with cognitive control, should mean there are major changes in reasoning capacities. If this is the case we cannot expect adolescents to have mature problem solving abilities or be able to make mature judgements about their decisions.

Another consistent problem is how to deal with individual differences that suggest a very large range within an age group. Some 8-year-olds may have brain responses like adults while many other children are different until age 18 years. This may be the clue to the long term question of considerable differences in emotional sophistication, such as empathy responses which we already associate with ventral and medial prefrontal cortex (Damasio, 2000; Hopkins, Dywan, & Segalowitz, 2002; Spinella, 2002). However, we must also be careful that what we are seeing as heterogeneous results in children is not just a function of greater day-to-day variability. Consistent responses that vary over time are not a result of lower SNR but of true lability. The appropriate control for this is careful attention to motivational factors and task instructions.

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