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SARA MÄÄTTÄ

Event-Related Potential Studies on Novelty Processing and Distractibility

Doctoral dissertation

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ABSTRACT

Distractibility can be defined as a deficit in which orientation towards irrelevant or unimportant stimuli cannot be inhibited. Children are more easily distracted by unexpected stimuli than adults. Enhanced distractibility due to abnormal involuntary attention may also be a symptom of several neuropsychiatric disorders, such as attention deficit hyperactivity disorder or depression.

The aim of this work was 1) to investigate the differences of novelty processing between children and adults to find electrophysiological indices of age-related improvement in resistance to distraction, and 2) to investigate the brain physiology underlying enhanced distractibility in adolescence. Therefore, four different research paradigms were used: novelty-elicited event-related potentials (ERPs) were studied in healthy children and adults in unattended and attended conditions, and the differences in involuntary and voluntary allocation of attentional resources were studied in easily distractible and non-distractible adolescents.

This study showed that the gross morphology of the ERPs elicited by novel stimuli was similar in children and adults, suggesting that processing of novel acoustic information is essentially similar across the age groups. However, the topographic differences in novelty-elicited ERPs between children and adults might reflect an age-related change in the activation of cortical networks associated with orienting to novel events. Also, it was found that the adults are better able to maintain their attentional focus even in the presence of unexpected stimuli, whereas children show attention-independent automatic processing of such stimuli. On the whole, these findings suggest an age-related change in activity in the frontal part of the brain. Given that attention processes in children are characterized by distractibility and less persistence, these findings can be considered to bring insight not only to the development of attentional brain functions, but also to the functional basis of increased distractibility

The second major finding was that enhanced distractibility in adolescence might be associated with deficits in early stages of information processing, probably already in the selection of stimuli into conscious processing. In addition, distractible adolescents seem to allocate proportionately more attentional resources to the irrelevant stimuli and less to the relevant stimuli than the attentive adolescents.

The results of this thesis contribute to the elucidation of the neural basis of distractibility. Addressing the issue of distractibility is not just of academic interest, but it may also have clinical applications.

National Library of Medicine Classification: QT 34, WL 102, WS 105.5.C7, WS 350.6, WS 462

Medical Subject Headings: adolescent; attention; attention deficit and disruptive behavior disorders/physiopathology; brain/physiology; cognitive science; electrophysiology; evoked potentials; nervous system physiology; neurophysiology

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Kuopio, November 2005

Sara Määttä

ABBREVIATIONS AND SYMBOLS

ADHD	attention deficit hyperactivity disorder
ANOVA	analysis of variance
BAEP	brainstem auditory evoked potential
EEG	electroencephalogram
ERP	event-related potential
ISI	inter-stimulus interval
ITI	inter-trial interval
IQ	intelligence quotient
LLAEP	long latency auditory evoked potential
MLAEP	middle latency auditory evoked potential
Nc	negative component
Nd	negative difference
PN	processing negativity
OR	orienting response
RON	reorienting negativity
RT	reaction time
WAIS-R	Wechsler Intelligence Scale for Adults- revised
WMS	Wechsler Memory Scale

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred in the text by their roman numerals.

I **Määttä S, Saavalainen P, Könönen M, Pääkkönen A, Muraja-Murro A, Partanen J:** Processing of highly novel auditory events in children and adults: an event-related potential study. Neuroreport. 2005 Sep 8;16(13):1443-46.

II **Määttä S, Pääkkönen A, Saavalainen P, Partanen J:** Selective attention event-related potential effects from auditory novel stimuli in children and adults. Clin Neurophysiol. 2005 Jan;116(1):129-41.

III **Määttä S, Saavalainen P, Herrgård E, Pääkkönen A, Luoma L, Laukkanen E, Partanen J:** Event-related potentials to elementary auditory input in distractible adolescents. Clin Neurophysiol. 2005 Jan;116(1):142-50.

IV **Määttä S, Herrgård E, Saavalainen P, Pääkkönen A, Könönen M, Luoma L, Laukkanen E, Yppärilä H, Partanen J:** P3 amplitude and time-on-task effects in distractible adolescents. Clin Neurophysiol. 2005 Sep;116(9):2175-83.

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APPENDIX: ORIGINAL PUBLICATIONS

CHAPTER I

INTRODUCTION

The directivity and selectivity of mental processes is usually termed attention in psychology (Luria 1973). The central problem of attention is - given the limited capacity of the attentional system - how the information processing system copes with the vast quantities of information arriving at any given moment. Limited processing capacity entails that there is invariably competition for attention. The entry of information to the attentional system is controlled by two types of processes: active selection and breakthrough of the unattended (James 1890). The first is a top-down (cognitive) process, and the second is a bottom-up (stimulus-driven) process that enables the evaluation of those potentially important events that are not currently selected by the first mechanism. The dynamic interaction of these processes controls how and to what we pay attention in the environment (Corbetta and Shulman 2002). If the top-down processes dominate one's attention, one may not react to vitally important events occurring outside the focus of attention. On the other hand, if bottom-up processes can too easily catch one's attention, then one's behavior appears fragmented, making goal-directed actions less effective (Escera et al 2000).

Distractibility refers to the inability to maintain attention, due to shifting from one area or topic to another with minimal provocation. In other words, it refers to an inability to control what one pays attention to. Children are more easily distracted by unexpected stimuli than adults, and improved resistance to distraction with increasing age plays a central role on the development of selective attention (Dempster 1993; Lane and Pearson 1982; Ruff and Capozzoli 2003). Distractibility may also be a manifestation of organic impairment (Kaipio et al 1999; Kaipio et al 2000), or it may be a part of a functional disorder such as attention deficit hyperactivity disorder (Barkley 1997; Douglas 1983; Kelly and Aylward 1992) or schizophrenia (Barch et al 1999; Harvey et al 1986).

Ever since Berger (1929) demonstrated that it is possible to record the electrical activity of the brain with electrodes placed on the surface of the scalp, there has been considerable interest in the relationship between these recordings and psychological processes. The recent research has concentrated on those aspects of the electrical potentials that are specifically time-locked to events, i.e. to event-related potentials (ERPs). ERPs are small electrical potentials that result from a change in the ongoing electrical activity of neuronal networks in response to a sensory stimulation or as a result of a cognitive process, reflecting real-time neuronal functioning.

Behavioral indices can at best provide only indirect evidence on age-related changes in attentional capacity, and have failed to address systematically the fundamental question of what is developing in the child that would account for the improved resistance to distraction. Likewise, the brain mechanisms of increased distractibility remain poorly understood. ERPs offer an electrophysiological method for studying human brain maturation associated with different aspects of perceptual and cognitive development (Courchesne 1990). ERPs can also provide valuable information about abnormal cognitive development and attentional deficits (Gumenyuk 2005). To elucidate these issues, the present work investigated the brain mechanisms involved in the processing of novel acoustic information, and electrophysiological indices of increased distractibility.

CHAPTER II

REVIEW OF THE LITERATURE

2.1 Attention

The human brain does not have a sufficient capacity to allow the conscious processing of all stimulus information that simultaneously impinges on the various senses. Attention filters this information and selects particular objects or events for further analysis. Attentional processes can be either voluntary or involuntary (James 1890). Maintaining a goal-directed behavior requires selectively attending to a subset of the sensory input at the expense of the rest of the input (voluntary attention). At the same time, a surveillance mechanism must be in operation, so that those potentially important deviant or novel events that are not currently selected by the voluntary mechanism, are available for conscious processing (involuntary attention).

2.1.1 Involuntary attention and the orienting reflex

Involuntary attention occurs when attention is attracted by sudden and unexpected changes in the subject's immediate environment. Such events take high priority in the brain, and are processed at the expense of ongoing behavior and neural activity (Corbetta and Shulman 2002). Involuntary attention to novel events thus plays a critical role in adaptation and learning (Sokolov 1963). The duration of involuntary attention to the stimulus that causes the attention switch usually depends on the time needed for stimulus recognition and evaluation (Näätänen 1992).

Stimuli that elicit involuntary attention also tend to elicit the orienting reflex (OR) (Sokolov 1963). The concept of the OR has been central in many theories of involuntary attention. The OR is a rapid response to new (never experienced before), unexpected (out of context), or unpredictable stimuli. It functions as a "what-is-it" detector, involuntarily capturing attention and facilitating further processing of the novel stimuli (Pavlov 1927). The OR is manifested as a complex pattern of skeletal, physiological and behavioral changes. These include the galvanic skin response, respiratory pause, reciprocal blood volume changes in the head and fingers, electroencephalographic (EEG) changes toward faster and lower amplitude activity, pupil dilatation, eye movements, changes in position of the body, and heart rate. From an anatomical perspective, the mechanism mediating orienting is highly complex, including several regions of the frontal lobes, but also more posterior regions (Daffner et al 2000a; Daffner et al 2000b; Daffner et al 1998; Daffner et al 2003; Knight 1984;

Knight et al 1995; Knight and Scabini 1998). The importance of this reflex can be seen from studies showing that infants (Morrongiello and Clifton 1984) and even near-term fetuses (Lecanuet et al 1992) show the ability to orient to some sounds.

One of the hallmarks of the OR is its rapid habituation: as the stimulus loses its novelty with repeated presentation, the size of the OR decreases (Sokolov 1963). This habituation is proposed to indicate that there is some type of memory for the prior events that modifies the response to the repeated incidences (Sokolov 1969). Another essential feature of the OR distinguishing it from the general "arousal reaction" is that it may be highly directive and selective in character, thus creating the basis for directive and selective, organized behavior (Luria 1973).

2.1.2 Selective attention

Selective attention refers to the ability to voluntarily select particular inputs for conscious processing and to ignore other inputs. This requires an ability to differentiate between relevant and irrelevant stimuli, select the relevant stimuli for further processing, inhibit processing of the irrelevant stimuli, and sustain focused attention on the selected stimulus stream over some period of time. Current neuropsychological theories specify a network of cortical areas that underlie auditory selective attention, including posterior parietal, prefrontal and cingulated regions (Mesulam 1981).

Many models of selective attention assume that the amount of information that can be focused on at any specific moment is limited, but the locus of selection of relevant from irrelevant information and the nature of processing of the ignored or irrelevant information remain a matter of speculation (Broadbent 1958; Deutsch and Deutsch 1963; Norman 1975; Treisman 1960). Some have argued for early selection mechanisms, in which relevant information is selected from the irrelevant based on physical attributes, and only the selected stimuli are processed at higher levels (Broadbent 1958). Other models have argued that selection occurs late in the sequence, suggesting that all stimuli are fully processed before any selection occurs (Deutsch and Deutsch 1963; Treisman 1960). Proponents of both early and late selection models often assume that the representation of irrelevant information dissipates passively over time as resources are directed at processing the relevant information.

Traditionally, developmental theories emphasize the role of changes in the capacity to store and process information in accounting for cognitive development, and age-related improvements in the voluntary deployment of attentional selection are considered among the most profound advances in information processing efficiency that take place as children grow older (Ridderinkhof and van der Stelt 2000). Such age-related differences are well documented in the behavioral developmental literature (for a review, see Lane and Pearson 1982), but psychophysiological studies on developmental changes in auditory selective attention are scarce (Berman and Friedman 1995; Coch et al 2005; Ridderinkhof and van der Stelt 2000; van der Stelt et al 1998).

2.1.3 Distractibility

Human behavior emerges from the interaction of the goals that people have and the stimuli that impinge on them. Responsive behavior should be based on relevant stimulus aspects whereas the processing of irrelevant stimuli must be inhibited.

Distractibility can be defined as a deficit in which orientation towards irrelevant or unimportant stimuli cannot be inhibited (Tecce et al 1976). Children are more easily distracted by unexpected stimuli than adults, and improved resistance to distraction is a major developmental dimension (Dempster 1993; Lane and Pearson 1982; Ruff and Capozzoli 2003). The basis of this developmental difference is ambiguous. It has been suggested to result either from a tendency of children to spend some of their attentional capacity in the processing of irrelevant stimuli or, alternatively, from children having more difficulty inhibiting responses to the irrelevant stimuli (Lane and Pearson 1982). The frontal lobes are heavily involved in interference regulation (Fuster 1997). Since the frontal lobes are the last to mature (Giedd 2004; Giedd et al 1999; Huttenlocher 1990), the development of frontal lobe functions is accounted for the development of attentional brain functions in children (Case 1992; Dempster 1993).

Patients with prefrontal lesions are easily distracted (Dempster 1993; Godefroy and Rousseaux 1996; Woods and Knight 1986), and there is a striking similarity of children's performance and the deficits shown by frontally damaged patients (for a review, see van der Molen 2000). Also other brain injuries (Kaipio et al 1999) and neurological and psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD) (e.g. Barkley 1997; Douglas 1983; Kelly and Aylward 1992), autism (Ehlers et al 1997), bipolar disorder (Wilder-Willis et al 2001) or schizophrenia (Barch et al 1999; Harvey et al 1986) affect the balance of attentional control, and symptoms of such states are usually described in terms of distractibility. Particularly in children with ADHD, inattention resulting from susceptibility to distraction is a core clinical feature (Kelly and Aylward 1992). ADHD is the most common neurobehavioral disorder in childhood and adolescence, affecting about 3-5% of children (American Psychiatric Association 1994; Airaksinen et al 2004) and up to now, the mechanisms of childhood and adolescence distractibility have been studied mostly in subjects with ADHD. However, the brain mechanisms of distractibility remain a matter of debate.

2.2 Auditory event-related potentials (ERPs)

2.2.1 ERP definition and classification

ERPs are voltage changes time-locked to some physical or mental occurrence in the ongoing electrical brain activity (recorded as EEG). They represent the field potentials generated by synchronous nerve cell activity at different sites of the cerebral cortex, and in the sense organs and pathways leading to the brain. When a large population of elongated neurons having a similar orientation is activated concurrently, the summated field may be sufficient to be recordable as ERPs and can be recorded from the human scalp and extracted from the ongoing EEG by means of filtering and signal averaging (Hillyard et al 1995; Fabiani et al 2000). At the cellular level, ERPs are generated as a consequence of the flow of ionic currents during synaptic activity. It is commonly believed that most scalp ERPs result from the summation of postsynaptic potentials (Allison et al 1986). Depending on the type of sensory stimulus, the ERPs can be divided into somatosensory, visual or auditory ERPs. This thesis concerns the auditory modality.

ERPs typically consist of a sequence of positive and negative waves or peaks. The labels given to the peaks of an ERP usually include descriptors of polarity and latency or ordinal latency (i.e. P300 refers to a positive peak with a latency of 300 ms, or P3 to the 3rd positive peak in the waveform). According to their timing relative to stimulus onset, the auditory ERPs can be divided into short-latency (brainstem auditory evoked potential, BAEP, 0-12 ms after stimulus onset) (Jewett and Williston 1971), or middle-latency (middle-latency auditory evoked potentials, MLAEP, 10-70 ms after stimulus onset) (Picton et al 1974), and long-latency (long-latency auditory evoked potentials, LLAEP, > 50 ms after stimulus onset) responses. The BAEP is generated in multiple structures from the auditory (8th) nerve through the thalamus (Vaughan and Arezzo 1988), the MLAEP is generated by the early afferent activation of the primary auditory cortices (Celesia 1976), and the LLAEP reflect the activation of neocortex and limbic structures (Näätänen 1992). These waveforms contain components that span in continuum between the exogenous and endogenous potentials. Exogenous ERP components are determined by the physical characteristics of the stimulus (e.g. frequency, intensity, duration) and change their properties only in relation to stimulus features. The endogenous components, in contrast, reflect internally generated mental events related to the cognitive assessment of the stimulus, and are only partially related to physical stimulus features. They also depend very much on the experimental paradigm used. Both short-latency and middle latency ERPs are thought to be exogenous, whereas the LLAEPs contain both exogenous and endogenous components. A characteristic sequence of voltage deflections at the scalp triggered by an auditory stimulus is shown in Figure 1.

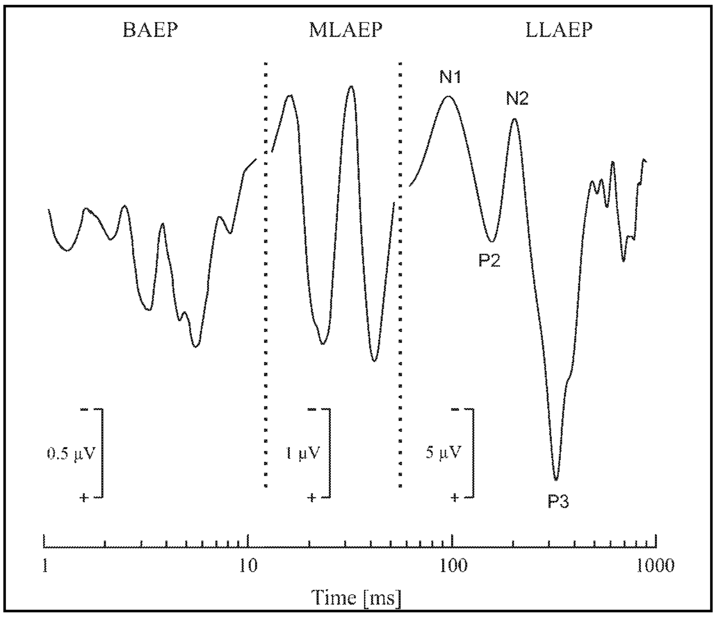

Figure 1: A characteristic sequence of voltage deflections at the scalp triggered by an auditory stimulus.

ERPs offer a psychophysiological method for studying attentional processes, language and memory functions, and human brain maturation, yielding information not available from behavioral studies. ERRs are recorded with specific study procedures, or paradigms, suitable for the aims of the study. In ERP studies of attention, perhaps the most commonly used experimental approach is the active oddball paradigm. In this paradigm, typically two classes of stimuli are presented, one occurring frequently (standard) and the other occurring infrequently (target), and the subject is required to distinguish between the two stimuli and to respond to the stimuli that are pre-designated as targets. Variations of this paradigm include the passive oddball paradigm, in which the subject is instructed to ignore the stimuli, so-called novelty oddball paradigm, in which a third class of stimuli (novelty) are also presented intermixed with the standard and target stimuli, and a dichotic oddball paradigm, in which the stimuli are randomly interspersed between the two ears, the subject being instructed to direct his attention towards one ear and to ignore the stimuli arriving at the opposite ear.

The following chapters introduce the long-latency auditory ERPs that are relevant to this thesis.

2.2.2 N1

The N1 (or N100) wave of an ERP is a large negative deflection that occurs around 100 milliseconds and is maximally recorded in the central region. In the auditory modality, it is evoked by a relatively abrupt change in the acoustic surroundings. Instead of being a unitary event, it is a sum of several functionally distinct subcomponents (Näätänen and Picton 1987). The N1 reflects mainly the activation of the auditory cortices (Celesia 1976; Scherg and Von Cramon 1985; Vaughan and Ritter 1970; Wolpaw and Penry 1975) but also the activation of the frontal lobes (Alcaini et al 1994; Hari et al 1982). The N1 is largely determined by the physical features of the stimulus (Näätänen and Picton 1987). However, one of the sub-components, the so-called "non-specific component" (or "vertex response") is presumed to reflect activation of orienting networks of the brain (Näätänen and Picton 1987).

When the stimulus is repeated, the N1 response decreases in amplitude, and the more rapidly the stimuli are delivered, the faster and more pronounced is the decrement (Fruhstorfer et al 1970). A large N1 is again generated if the stimulation is ceased for several seconds (Alcaini et al 1994; Hari et al 1982) or a large change occurs in the stimulus sequence (Alho et al 1998; Escera et al 1998). The exact physiological mechanisms of this decrement are unknown; however, it has been suggested to result from the refractoriness of the activated neural populations to further stimulation (Budd et al 1998; Näätänen and Picton 1987), or alternatively, from inhibitory processes (Sable et al 2004). The subcomponents of N1 react very differently to the inter-stimulus interval (ISI): the recovery time of the non-specific component is very long (Näätänen 1992; Näätänen and Picton 1987), whereas the stimulus-specific part of the N1 recovers fully in about 10 seconds (Hari et al 1987). Thus, the exceptionally large N1 occurring after a long interval (for example, to the first stimulus in a train) is mainly due to a very large non-specific N1, which is not elicited by the subsequent stimuli (Näätänen and Picton 1987).

There are progressive changes in the morphology and distribution of N1 across the age groups (Pang and Taylor 2000), and the subcomponents of the N1 mature along different timelines (Bruneau et al 1997; Pang and Taylor 2000). The general pattern of results indicates a smaller, later and more posteriorly distributed N1 in children than in adults. Moreover, in children younger than 7-9 years, the N1 is sometimes difficult to identify (Bruneau et al 1997; Martin et al 1988a; Ponton et al 2000). Children's N1 may also be replaced by a prominent negativity at the N2 latency range, particularly when stimuli are presented at short stimulus intervals (Ceponiene et al 1998; Coch et al 2005; Takeshita et al 2002). The relationship of this N2 component and the adult N1 is not clear.

2.2.3 Processing negativity (PN) and negative difference (Nd)

ERPs elicited by attended auditory stimuli that differ from unattended stimuli in location or pitch are negatively displaced in relation to ERPs elicited by unattended stimuli. This attention effect begins at the time window of the N1 (first described by Hillyard et al 1973) and may last for several hundred milliseconds (Näätänen et al 1978). It is attributed to a slow endogenous component called processing negativity (PN) and interpreted as an electrocortical reflection of selective attention. The PN is most commonly operationalized as the negativity derived by subtracting the ERP of unattended stimuli from the ERP produced by the same stimuli when attended (termed Nd by Hansen and Hillyard 1980). Attended stimuli (both standard and target) elicit PN, but also stimuli to be ignored elicit some PN (Hari et al 1989), at least if they physically resemble those to be attended (Alho et al 1986). As the irrelevant stimuli become more similar to the relevant stimuli, the amplitude of PN to irrelevant stimuli becomes larger and the duration longer (Alho et al 1987). Its onset latency depends on the ISI (Hansen and Hillyard 1984; Parasuraman 1980), so that with short ISIs, PN onset occurs early enough to overlap the N1 amplitude and thus enhance its amplitude (Näätänen and Michie 1979). Currently, the PN is thought to consist of at least two separate components, the earlier frontocentral PN component commencing at the N1 time window, and the later PN that is maximal at frontal leads at 300-400 ms (Giard et al 1988; Hansen and Hillyard 1980; Hansen and Hillyard 1984; Michie et al 1990; Michie et al 1993; Näätänen 1982). The early PN is suggested to reflect a matching process between the sensory features of the stimulus and an attentional trace, a voluntarily maintained neuronal representation of the physical features defining stimuli from the relevant source. The late frontal component of the PN reflects the selective rehearsal and maintenance of the attentional trace (Näätänen 1982; Näätänen 1990; Näätänen and Picton 1987).

Children have shown clear signs of selective attention as indicated by enhanced N1/PN amplitudes to stimuli in the attended channel. However, there is a developmental progression in both the latency and amplitude of the early aspect of the Nd waveform – its amplitude increases and latency decreases with increments in chronological age (Berman and Friedman 1995), and its topography is more posterior (Berman and Friedman 1995; Coch et al 2005) and for linguistic stimuli more left-lateralized in adults than in children (Coch et al 2005).

2.2.4 N2 components

The label N2 is used to refer to a family of negative components elicited by deviant stimuli that are similar in latency (at about 200 ms) and whose scalp distribution and functional significance vary according to stimulus modality and experimental manipulations (Näätänen and Picton 1986). The N2 elicited by task-irrelevant stimulus changes may be related to automatic processes (mismatch negativity, "basic N2" and sleep N2), whereas the N2 elicited during discrimination and classification tasks (N2b, N2c, omission N2 and detection N2) may be associated with controlled processes (Näätänen and Picton 1986).

The mismatch negativity (MMN; in earlier days called the N2a) is a frontal negativity at around 100-200 ms. It is generated automatically whenever the stimulus deviates physically from the immediately preceding context (Näätänen et al 1978; Näätänen and Michie 1979; Sams et al 1983). The MMN is commonly derived by subtracting the ERP to the standard stimulus from that to the deviant stimulus The MMN is thought to reflect the mismatch between a trace in a sensory memory (of the standard stimulus) and the representation of the current stimulus to which the trace is compared, and is considered to be an index of the preattentive stage of auditory information processing (Näätänen 1992). There is also evidence supporting the notion that the process generating the MMN may be associated with involuntary attention switching (Schroger 1996). The MMN is generated mainly in the auditory cortex in the temporal lobes (Hari et al 1984; Scherg 1989). Furthermore, a frontal MMN generator (Alain et al 1998), probably reflecting attention switch to a change in repetitive auditory stimuli (Rinne et al 2000), has also been implicated. The MMN appears to be an early developing response which can be observed even in newborn (Cheour-Luhtanen et al 1995; Cheour-Luhtanen et al 1996) and there are no big differences in the MMN parameters between adults and school-aged children (Kraus et al 1993). In addition to the MMN, so-called “basic” N2 may also be elicited automatically. This component is clearly observed in children, but it is not commonly seen in adults (Karhu et al 1997). It may be observed in addition to N1 in response to both the standard and rare stimuli during oddball task (Johnstone et al 1996), and even in response to repetitive homogenous stimuli (Näätänen and Picton 1986). Thus, the children’s N2 component may represent a discriminative process (Johnstone et al 1996), which is supposed to be automatic and preattentive (Takeshita et al 2002), and might play an important role in auditory processing until efficient adult-level cortical networks are established.

In the attended conditions, the MMN is overlapped by the N2b, a sharp negative component with a fronto-central or central topography, often preceding P3 component. The generators of N2b are located in superior temporal gyrus, precuneatus and medial anterior cingulated structures (Anderer et al 2004). The N2b requires conscious perception of the stimulus, and is taken to reflect the stimulus comparison that is involved in discrimination between target and non-target stimuli (Näätänen and Picton 1986). The N2b amplitude is larger and the latency longer when the target is more difficult to discriminate (Fitzgerald and Picton 1983). Since the N2b correlates with reaction times, it has been proposed to reflect target selection and decision process that controls behavioral responses in discrimination tasks (Ritter et al 1979). It has also been suggested to reflect the awareness of the subject that an unexpected event has occurred (Leppert et al 2003).

The preceding paragraphs introduced some of the N2 components in the context of automatic and controlled processing. It is not clear which of the N2 components is the one that is evoked in response to novel stimuli.

2.2.5 P3 responses

Auditory P3(or P300), a positive deflection occurring at about 300 ms from stimulus onset, is one of the most widely studied components of the ERP. It is generated by the activation of multiple neocortical and limbic regions, and has two functionally different components: the earlier P3a that is maximal over frontocentral regions, and the later P3b that is maximal at posterior scalp locations (Squires et al 1975a).

2.2.5.1 P3b

The P3b is parietocentral positivity that occurs when a subject detects an informative task relevant stimulus (first decribed by Desmedt et al 1965; Sutton et al 1965). It is most commonly elicited in an oddball paradigm when a subject detects an occasional target stimulus in a regular train of standard stimuli. The P3 probably represent concurrent activity in multiple regions of the brain. Depth electrode recordings (Halgren et al 1995a; Halgren et al 1995b; Halgren et al 1980), lesion studies (Johnson 1989; Verleger et al 1994) and magnetic field studies (Alho et al 1986; Horn et al 2003; McCarthy et al 1997; Menon et al 1997; Opitz et al 1999; Stevens et al 2000) suggest that at least some portion of the P3b is generated in networks that compose the temporal-parietal neocortical areas and higher limbic structures.

The major theoretical interpretation of the P3b component is that it indexes updating of activity in corticolimbic circuits in processes requiring attention and working memory (Donchin 1981; Donchin and Coles 1988). Alternative hypotheses suggest that the P3 is related to the end of processing periods (Desmedt 1981; Verleger 1988). The P3 has a latency to peak of anywhere from 300 to 1000 ms, depending on task complexity and the clinical sample tested. A frequently observed phenomenon is that the P3 latency increases when categorization of the stimulus becomes more difficult. A general consensus seems to be that P3b is evoked after the stimulus has been evaluated (Kok 2001). Thus, the latency of P3 has been regarded as a measure of stimulus evaluation time (Kutas et al 1977). Although P3b is not exclusively a measure of selective attention, it is often used as a measure of allocation of attentional resources (e.g. Donchin and Coles 1988).

Three important determinants of P3b amplitude are stimulus probability, task difficulty and task relevance. Decreases in the probability of the target stimulus produces increases in P3 amplitude (Duncan-Johnson and Donchin 1977; Squires et al 1977). With sufficient increases in task difficulty, P3b amplitude decreases (Isreal et al 1980; Polich 1987; Wickens et al 1983). Task relevance is usually defined as the amount of attention that is paid to the stimulus. P3b amplitude is proportional to the amount of attentional resources devoted to a given task (Wickens et al 1983), and many studies have shown that P3 is larger to attended than unattended stimuli (Donchin and Coles 1988; Hillyard et al 1973; Squires et al 1977; for a review, see Picton 1992; Polich 1996).

An important finding regarding P3 is that its amplitude declines in response to repeated stimulation (Lammers and Badia 1989; Lew and Polich 1993; Lindin et al 2004; Polich and McIsaac 1994; Romero and Polich 1996). The factors responsible for the time-on-task effect on P3 amplitude remain a matter of speculation, but it has been suggested that the reduction of the P3 at least partly reflects a change in the amount of attentional resources allocated to the task (Carrillo-de-la-Pena and Garcia-Larrea 1999; Lammers and Badia 1989; Lew and Polich 1993).

A P3-like parietal positivity can be recognized during oddball paradigms from the age of 5 years. In children, the P3 latency decreases with increasing age until puberty, when it stabilizes (Fuchigami et al 1995; Johnstone et al 1996; Martin et al 1988a; Martin et al 1988b; Polich et al 1990). The amplitude of the P3 increases with increasing age until about 13 years of age, after which it may decrease slightly to normal adult values (Courchesne 1978a; Goodin et al 1978; Martin et al 1988b; Polich et al 1990), suggesting that target detection may become less demanding as children grow older.

Changes in the latency, amplitude and topography of the P3b correlate with clinical findings in a wide range of disorders and brain injuries. Several important childhood and adulthood neuropsychiatric disorders, such as ADHD, oppositional defiant disorder, and conduct disorder have been associated with reduced P3b amplitude (Bauer and Hesselbrock 1999a; Bauer and Hesselbrock 1999b; Bauer and Hesselbrock 2003; Iacono et al 2003). A reduced P3 amplitude also appears to be associated with a risk for alcoholism and substance abuse in general (Iacono et al 2003), and with depression and schizophrenia (Blackwood et al 1987), as well as with organic brain lesions (Daffner et al 2003; Rugg et al 1988).

2.2.5.2 P3a

The P3a (at around 300 ms) is a frontocentrally maximal positive ERP wave elicited by deviant or unexpected events (Courchesne et al 1975; Squires et al 1975a), and it is considered as an electrophysiological marker of the attentional switching, i.e. the OR (Squires et al 1975b). P3a is generated by a complex cerebral network, including the prefrontal, cingulate, temporo-parietal, and hippocampal regions (Alho et al 1998; Baudena et al 1995; Halgren et al 1995a; Knight 1996; Knight 1984; Knight et al 1989; Mecklinger and Ullsperger 1995) and it is recorded over widespread anterior and posterior scalp sites (Knight 1984; Knight et al 1989). It has been distinguished from P3b by a shorter peak latency, a more frontally oriented scalp topography and different elicitation conditions (Squires et al 1975a).

Different subcomponents for the P3a have been described depending on the study condition. In active or passive auditory task, the P3a elicited by novel events consists of frontal and posterior components (Fabiani and Friedman 1995; Friedman et al 2001; Friedman et al 1998), of which the frontal P3a response is suggested to reflect the allocation of attentional resources to novel stimuli and the posterior component stimulus categorization (Cycowicz and Friedman 1997; Friedman et al 1998; Friedman and Simpson 1994), or the updating of one's internal model of the environment to take into account the novel event (Daffner et al 2003). In the active condition, novel tones might also elicit a second, more posterior P3 (the $P3_2$) possibly reflecting semantic processes, such as an attempt to categorize and/or to name the stimulus that had just been presented (Cycowicz and Friedman 1997; Friedman et al 1993). Alternatively, the P3a elicited by attention-capturing stimuli originating from the unattended source (mainly so-called "distraction" paradigms, but also in a passive condition), is composed the early P3a (eP3a) and late P3a (lP3a) (Escera et al 1998). The eP3a (maximal at vertex, strongly diminishing posteriorly and laterally) is suggested to reflect automatic detection of the violation of a multimodal neural model of the existing world (Yamaguchi and Knight 1992) and the lP3 (maximal frontally) the actual attention switch (Escera et al 1998).

In children, novel sounds elicit a fronto-centrally predominant P3a suggesting that the brain mechanisms responsible for processing novel information are functional at least by the time children are ready for school (Ceponiene et al 2004; Cycowicz and Friedman 1997; Cycowicz et al 1996; Gumenyuk et al 2001). However, the subcomponents of the P3a show a different maturational course. From the age of seven, the eP3a is distributed similarly as in adults, whereas the lP3 lacks the frontality characteristic of the adult lP3a response. This pattern of P3a in children suggests that that the processes involved in the orientation of attention (as assessed by the eP3a) mature early, but those underlying the attentional switch (as assessed by lP3a) do not (Ceponiene et al 2004).

The P3a is affected in several psychiatric and neurological disorders, in which increased distractibility is a common impairment. An enhanced P3a amplitude over the left frontal region has been found in chronic alcoholism (Polo et al 2003). An enhanced lP3a are found in children with depression (Lepisto et al 2004) and ADHD (Gumenyuk et al 2005). In addition, patients with closed head injuries show larger P3a amplitudes than control subjects (Kaipio et al 1999; Kaipio et al 2000).

2.2.6 Late negativities elicited by novel stimuli

The negative component (Nc), lasting from 300 to 1000 ms was initially considered to be a sign of enhanced auditory and visual attention since it was elicited in response to surprising, interesting or important stimuli (Courchesne 1978b; Courchesne 1990). Later, it was found that also repetitive, infrequent stimuli could elicit Nc if these stimuli were attention getting and attended to (Ciesielski et al 1990). Therefore, the Nc is suggested to reflect processing of stimuli that engage one's attention and induce more extensive cognitive stimulus assessment (Courchesne 1990). A similar late negativity was found when subjects had to reorient their attention back to a task after distraction (Schroger and Wolff 1998). This negativity was called the reorienting negativity (RON) (Schroger and Wolff 1998), and it was suggested to reflect activation of the prefrontal cortex networks controlling the re-direction of attention. It was absent in a passive condition (Schroger et al 2000; Schroger and Wolff 1998). It has multiple generators, probably located in frontal areas (Schroger et al 2000). The magnetoencephalogram data suggests that the temporal lobes might also contribute to this negativity (Gumenyuk et al 2001). Being of comparable latency and scalp topography, the Nc and RON might reflect similar processes (Kushnerenko 2003). The late negativity to novel sounds consist of two peaks in infants (Kushnerenko et al 2002) and adults (Escera et al 2001), the later phase being larger to novel than to deviant stimuli (Kushnerenko 2003). The earlier component appears to reflect cognitive attentive processing of salient stimuli and the later component might reflect reorienting after distraction (Ceponiene et al 2004).

The late negative component (Nc/RON) can be observed as early as in kindergarten children of 5-6 years (Wetzel et al 2004), is largest in amplitude during childhood and diminishes by young adulthood (Courchesne 1990). Like in adults, it is largest at frontocentral leads in children, but in children it spreads over central and parietal areas (Wetzel et al 2004). The timing is similar in children and adults (Wetzel et al 2004).

CHAPTER III

AIMS OF THE STUDY

This study focused on two related issues. First, it aimed to investigate the differences of novelty processing between children and adults, and second, to examine the neural mechanism of distractibility in adolescence. The specific aims of the studies were:

I To study the differences in processing of unattended novel auditory information between children and adults.

II To assess differences between children and adults in processing novel auditory information in the attended and unattended channels.

III To study the orienting to non-attended tones in distractible adolescents with special reference to misallocation of attentional resources to irrelevant information.

IV To examine the evaluation processes of target stimuli in a stream of attended tones in distractible adolescents as a function of time-on-task.

CHAPTER IV

SUBJECTS AND METHODS

4.1 Subjects and their neuropsychological evaluation

All subjects participated voluntarily in the experiment, and informed written consent was obtained from the adult subjects, and from the children's parents. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Kuopio University Hospital Research Ethical Committee.

4.1.1 Children and adults (Studies I and II)

A random sample of twenty normal children (aged 8–9 years, mean 9.3 years, 4 boys) and 10 normal healthy adults (aged 22-28 years, mean 24.9 years, 2 male) were enrolled in the investigation. The children were volunteers recruited from a local elementary school and the adults were medical students from the University of Kuopio. None of the subjects reported a history of significant psychiatric or neurological disease or severe head injury, and none was taking any medication that affects the central nervous system. All subjects were right-handed. In children, the handedness was determined by the report of their teacher (teacher's questionnaire) and in adult subjects, by their own report. The children attended normal classes, and according to their teacher, none of them had any learning difficulties. To obtain valid measures of attention and executive functions of the children, three subtests (Arithmetic, Digit span, Coding) of the Wechsler Intelligence Test for Children – Revised (Wechsler 1984) and six subtests (Statue, Tower, Knock and Tap, Visual attention, Auditory attention and response set, Design fluency) of NEPSY (Korkman 1997), were administered. All children performed within the normal range on all attentional tests.

4.1.2 Adolescents (Studies III and IV)

The adolescents were participants of a follow-up study of children born preterm (at $\leq$ 32 weeks of gestational age) and their control children born in Kuopio University Hospital between 1984 and 1986. At the age of 16, a total of 71 adolescents were investigated. Subjects with a major neurological disability (cerebral palsy, $n = 4$; mental retardation, $n = 1$) were excluded from ERP analyses. Thus, the subjects of studies III and IV were 66 healthy adolescents, whose growth and development had been followed up since they were born. None of these subjects had a history of significant psychiatric or neurological disease or head injury, and none was taking any medication that affects the central nervous system.

All adolescents were administered three neuropsychological tests: the Mental Control and the Letter-Number-Sequencing subtests of the Wechsler Memory Scale (WMS) III (Wechsler 1997), and the Stroop task: Color-Word-Interference (Golden 1978) (Table 1). All subjects were also administered the subtests Vocabulary, Information, Arithmetic and Digit Span of Wechsler Intelligence Scale for Adults – revised (WAIS-R) (Wechsler 1981) to calculate the verbal intelligence quotient (IQ). All adolescents had verbal IQ scores higher than 80; except for one distractible adolescent who had a verbal score of 75.

Table 1: Summary of neuropsychological tests used in the assessment of distractibility.

Test	Task	Requirements
Mental Control WMS III	Mental Control consists of subtests assessing the speed and accuracy of recall of overlearned information. The subject is e.g. told to say aloud numbers from 1 to 20, and count backwards from 20, and recite days of week or months forwards and backward. It also includes dual task demands (e.g. counting by sixes). Both time and number of correct answers is recorded.	Requires sustained attention and ability to concentrate.
Letter-Number Sequencing WMS III	The subject listens to an intermixed set of letters and numbers. The task for the subject is then to reorganize the numbers in ascending order and the letters in alphabetical order. The number of correct answers is recorded.	Successful responding to oral stimuli that involves handling of numbers and letters in a sequential fashion requires a non-distractible attention span.
Stroop: Color-Word Interference	The subject has to identify the colors of incongruent word, e.g. the word "red", written in green ink. The time is recorded.	Reading the word interferes with naming the color. This phenomenon is called Stroop effect, requiring inhibition of competing response.

The distractibility of the subjects was assessed with a sumscore, which was composed of the standard points of the Stroop Color-Word-Interference task (Golden 1978) and the two subtests (Mental Control and the Letter-Number-Sequencing) of the WMS III (Wechsler 1997). These tests are commonly used in assessment of attention. Based on the sum score of the three tests of attention, the adolescents were divided into two extreme groups for ERP analysis: a high distractibility group composed of 16 adolescents whose sum scores were among the lowest quarter, and the non-distractibility group of 16 adolescents whose sum scores were among the best quarter. The groups in Studies III and IV are slightly different, because two adolescents in the distractible group of Study III were excluded from Study IV because of technical problems. In Study III, the high distractibility group was composed of 16 right-handed adolescents (mean age 16 years; 11 boys) and the non-distractibility group of three left-handed and 13 right-handed (16 adolescents; mean age 16.07 years, 7 boys). In Study IV, the high distractibility group was composed of 16 right-handed adolescents (mean age 16.13 years; 12 boys) and the non-distractibility group of 14 right-handed and 2 left-handed adolescents (mean age 16.07 years, 7 boys) (Table 2).

Table 2: The distractibility sum score was composed of the standard scores of the three tests (the Wechsler Memory Scale (WMS) III: Mental Control, the WMS III: Letter-Number-Sequencing (Wechsler, 1997), and the Stroop task: color-word-interference (Golden, 1978).

	Study III		Study IV	
Test (mean, standard scores, SD)	Distractible adolescents	Non-distractible adolecents	Distractible adolescents	Non-distractible adolecents
Mental Control	9.63 (1.6)	14.56 (1.0)	9.1 (1.8)	14.4 (1.1)
Letter-Number Sequencing	4.81 (1.9)	10.06 (1.4)	5.4 (1.5)	10.1 (1.4)
Stroop	9.23 (1.2)	10.37 (0.5)	9.3 (1.3)	10.4 (0.5)
The distractibility sumscore	23.66 (2.7)	34.99 (1.4)	23.7 (2.5)	34.9 (1.4)

The neuropsychological assessment was administered by a clinical psychologist with no knowledge of the birth histories of the subjects. There was no difference between the distractible and non-distractible adolescents in their birth history (preterm versus full-term): in Study III, nine of the easily distractible and eight of the non-distractible adolescents belonged to the preterm group, and in Study IV, eight of the easily distractible adolescents and seven of the non-distractible adolescents belonged to the preterm study group. The handedness of the adolescents was determined by their own report.

4.2 Stimuli and experimental design

Four different stimulus paradigms were used in this study. The hearing level of each subject was tested at the beginning of the recording session using the same tone pips as in the experiment. Stimulus intensity was adjusted individually at 50 dB above the hearing level. The stimuli were delivered by headphones to the right ear (Studies III and IV) or to the right and left ears separately (Studies I and II).

Active and passive dichotic novelty oddball paradigm (Studies I and II)

The ERPs were elicited using a dichotic three-tone oddball paradigm with 86.8 % standard (800Hz), 10.8 % deviant/target (560 Hz) and 2.4 % novel tones. The duration of standard and deviant tones was 84 ms, including 7-ms rise and fall times. The novelty tones were six different complex 100-ms tone bursts including 2-ms rise and fall times (Figure 2). The order of the tones in the sequence and also their occurrence to right and left ears were semi-randomized. The number of stimuli was 520 and the inter-stimulus interval (ISI) was 1 s. The stimulus sequence was presented in three different recording conditions. In the first run, the subject was instructed to ignore the tones and to concentrate on watching a video (ignore condition, Study I). In the second and third run (the attended conditions, Study II), the subject was instructed to focus on the right or the left ear and to respond to each target stimuli on the attended side by pressing a button with their dominant (right) hand. Every other subject attended first to the left ear.

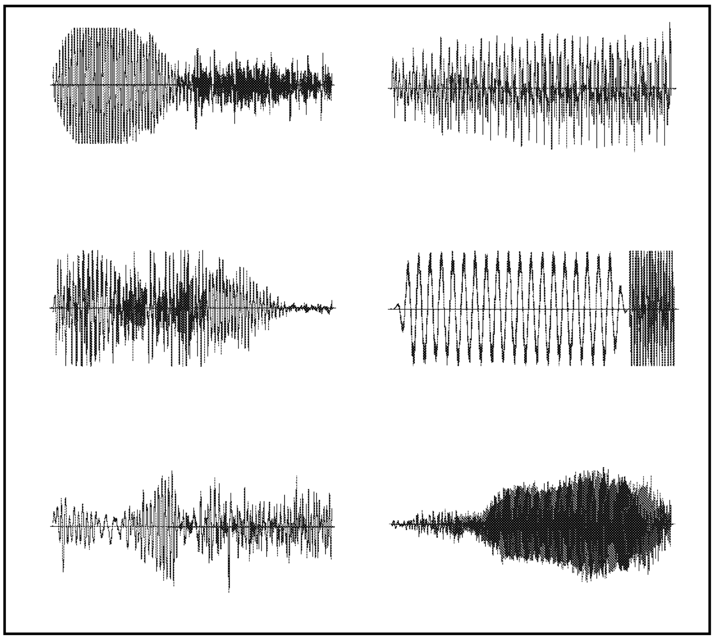

Figure 2: The waveforms of novel stimuli.

Habituation paradigm (Study III)
Tone pips (frequency 800 Hz, duration 84 ms including 7 ms rise and fall times) were delivered to the right ear in trains of four with an ISI of 1 s and an inter-train interval (ITI) of 12 s. During the 10-min recording session, the subject was instructed to ignore the tones and to concentrate on watching a video.

An active two-tone oddball paradigm (Study IV)
The P3 was measured using an auditory oddball paradigm with 85 % of standard (800 Hz) and 15 % of target (560 Hz) tones. The duration of each tone was 84 ms, including 7-ms rise and fall times. The number of stimuli was 520 and the ISI was 1 s. The duration of the experiment was 9 minutes. During the recording, the subjects were instructed to respond to each target stimuli by pressing a button.

4.3 EEG recording

The ERPs were recorded with a 60 channel electrode cap using Ag/AgCl electrodes (Figure 3). Electrode-skin impedances were kept below 5 kOhm. During the experiments, all electrodes were referred to the right mastoid. Potentials reflecting vertical eye movements and eye blinks were recorded between electrodes placed above and below the right eye. All signals were amplified and filtered by a Neuroscan Synamps amplifier (Neuroscan Inc., Virginia, USA) with a band pass of 0.5–50 Hz and digitized continuously at 250 Hz.

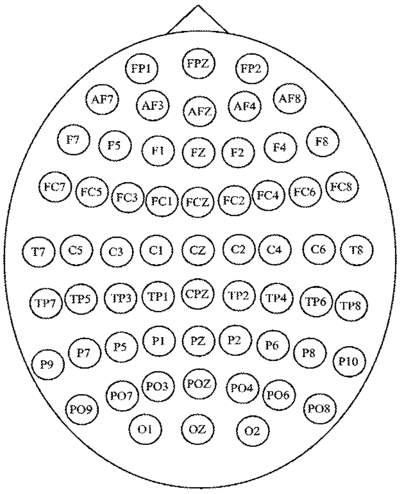

Figure 3: A schematic illustration of the extended 10-20 (the 10-10) system electrode array.

The continuous EEG was sampled to 1 second epochs, from –100 ms to 900 ms relative to the onset of each stimulus. Blink artefacts were reduced using a regression-based ocular artefact reduction algorithm (Semlitsch et al 1986). After that, epochs containing eye movement artefacts were rejected (rejection levels +75 μV and –75 μV). The corrected epoched data were averaged and filtered digitally with a low pass cut-off frequency at 20 Hz (3 dB point of 24 dB/octave roll-off) and the averages were aligned to a 100-ms pre-stimulus baseline. In Studies I and II, the data were re-referred off-line to the average of the potentials at electrode sites P9 and P10 in order to avoid any possible bias caused by the unilateral reference.

In Studies I and II, responses to each stimulus type were averaged separately for each subject. In Study III, the epoched data were averaged so that the responses to the first, second, third and fourth stimulus from each train were averaged separately (thus resulting in four averaged waveforms for each subject). In study IV, the responses to the target stimuli were averaged separately for the beginning (the 1st third), middle (the 2nd third), and end (the final third) of the stimulus sequence for each subject.

4.4 Data analysis

4.4.1 ERP analysis

The averaged responses were evaluated by measuring the amplitudes (Studies I-IV) and latencies (Studies II-IV) of the peaks of interest. The amplitudes and latencies of the ERP peaks were measured from the latency windows defined by the latency distribution of the peak of interest across the subjects. An automatic peak detection method combined with manual checking was used. The parameter selections for the ERP analyses are presented in Table 4.

Table 4: ERP analysis

	Electrode sites	**Paradigm and response waveforms**	**ERP peaks (latency range)**
Study I	F5, Fz, F4, C3, Cz, C4, P5, Pz, P6	a passive dichotic novelty oddball paradigm novel *minus* standard difference wave	P3a (200-320 ms in children, 200-300 ms in adults) $P3_2$ (320-420 ms in children, 300-400 ms in adults) Nc1 (450-600 ms in children and adults) Nc2 (600-800 ms in children and adults)
Study II	Fz, Fcz, Cz, Cpz, Pz	an active dichotic novelty oddball paradigm standard, target and novel tones	N1 (80-180 ms in children, 75-160 ms in adults) N2 (200-290 ms in children, 160-240 ms in adults) P3b (500-800 ms in children, 250-500 ms in adults) P3a (250-400 ms in children, 200-400 ms in adults)
Study III	C3, C1, Cz, C2, C4, Tp1, Cpz, Tp2, P5, P1, Pz, P2, P6, Po3, Poz, Po4	a habituation paradigm standard tones	N1 (80–160 ms) N2 (220-340 ms) P2 (160-240 ms) P3 (250-400 ms)
	F5, F1, Fz, F2, F4, Fc1, Fcz, Fc2, P5, P1, Pz, P2, P6, Po3, Poz, Po4	first stimulus of the experiment	P3 (250–400 ms)
Study IV	F1, Fz, F2 C3, Cz, C4, P1, Pz, P2	an active two-tone oddball paradigm target tones	P3 (300–500 ms)

4.4.2 Behavioral measures

In Studies II and III, the subjects were instructed to respond to each target stimuli by pressing a button. Pressing the button within 1000 ms interval after the target presentation was regarded as a hit, and the average reaction time (RT, in milliseconds) was computed for these trials. An incorrect button press after the standard or novel tone during this interval was classified as an error and a trial with no response as a miss.

4.4.3 Statistical analysis

The statistical analyses of all data were performed with the appropriate designs of the analysis of variance (ANOVA), and post hoc tests (Tukey's HSD in Study II, *t*-tests in Study III, and Helmert contrasts in Studies I and IV) were applied to determine the sources of the significant effects. The level of significance was set at $p < 0.05$. Statistical analyses were computed with the SPSS for Windows 10.0 or 11.0 statistical programs.

CHAPTER V

SUMMARY OF RESULTS

5.1 Processing of highly novel sounds in children and adults (Study I)

In Study I, differences in novelty detection between children and adults were examined by analyzing the late positive and negative ERP components evoked during a passive dichotic novelty oddball paradigm. The novel tones elicited a prominent biphasic P3 and Nc components in both age groups, i.e. the gross morphology of the ERPs was similar in children and adults. The topography of the P3 components differed between the two groups (group x anterior-posterior regions, F(2,56) = 5.676, p = 0.006 and F(2,56) = 10.524, p = 0.001 for P3a and $P3_2$, respectively) (Fig 4). In children, both P3 components showed a frontal maximum, whereas in adults, the P3a was maximal at central electrode sites and the $P3_2$ at parietal electrode sites. The Nc2 component was larger in children than in adults (F(1,28) = 11.250, p = 0.002).

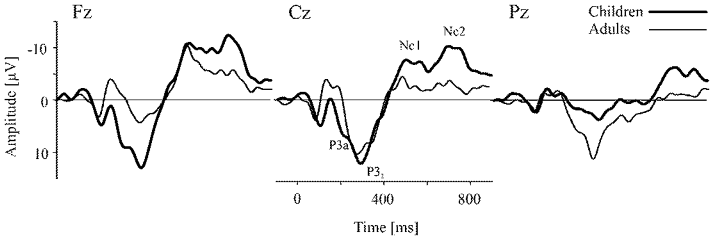

Figure 4: Grand-average difference waves (novelty *minus* standard) at Fz, Cz and Pz in children and adults.

5.2 Novelty processing in attended and unattended channels in children and adults (Study II)

In Study II, differences in selective attention between children and adults were studied, with emphasis on the processing of novel events in the attended and unattended channels. Subjects performed an active dichotic novelty oddball task. The performance data showed that the percentage of correct responses was smaller in children than in adults (F(1,28) = (27.932), p<0.001), and that the children made more errors than adults (F(1,28) = 6.868, p = 0.014).

The standard tones elicited an N1 component in both groups. The children also displayed a prominent N2 (Fig 5). In children, there was an attention-induced enhancement on both N1 (side of stimulation x attended side: F(1,19) = 8.871, p = 0.008) and N2 (side of stimulation x attended side: F(1,19) = 7.433, p = 0.013). In adults, the amplitude of N1 did not differ between the attended and the unattended sides.

The target tones elicited N1, N2 and P3 components in both groups. Adults showed a selective attention induced enhancement of the target elicited N2 (side of stimulation x attended side: F(1,9) = 15.405, p = 0.003) and P3b (side of stimulation x attended side: F(1,9) = 11.233, p = 0.009), whereas children showed attention-induced enhancement of P3 only (ear x attended side: F(1,19) = 41.170, p < 0.001) (Fig 5).

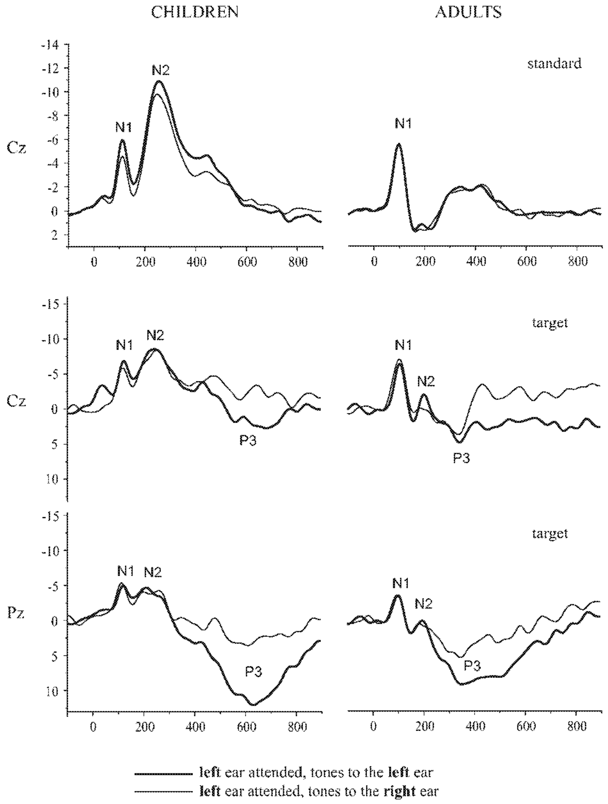

Figure 5: Grand-average ERP waveforms elicited by standard and target stimuli presented to the left ear in children and in adults.

The novel tones also elicited a sequence of deflection comprised of N1, N2 and P3 (Fig. 6). In children, novelty-elicited N2 responses were larger to the left ear stimuli irrespective of the direction of attention (main effect of side of stimulation: F(1,19) = 5.286, p = 0.033). Adults displayed enhanced novelty-elicited N2 amplitudes on the attended side (side of stimulation x attended side: F(1,9) = 6.663, p = 0.03).

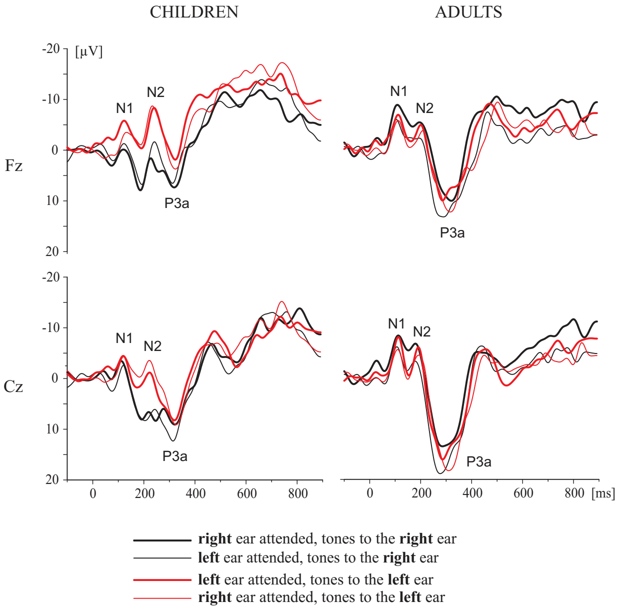

Figure 6: Grand-average ERP waveforms elicited by novel stimuli in children and in adults at Fz and Cz. In adults, responses to novel tones delivered to the attended ear were significantly larger than those delivered to the non-attended ear, whereas in children, novelty-elicited N2 responses were larger to left ear stimuli irrespective of the direction of attention.

5.3 N1 amplitude decrement as a function of repetition in easily distractible and non-distractible adolescents (Study III)

The third study examined the standard-tone elicited ERPs as a function of repetition in easily distractible and non-distractible adolescents. The standard stimuli were presented in trains of four stimuli. The N1 component of the ERP was clearly observed in response to all four stimuli of the train. The ANOVA with 2 groups x the first two tones yielded a significant group x tone interaction (F(1,30) = 4.308, p = 0.047). The amplitude of the N1 response to the first stimulus in the train was significantly larger in distractible adolescents than in the attentive group (p = 0.026), but the amplitude in response to the second stimulus in the train did not differ between the groups (Fig 7). Consequently, the difference between the N1 responses to first and the second stimulus was significantly larger in the distractible adolescents. The N2 was identifiable in response to the second, third and the fourth stimulus in the train. Its amplitude increased significantly with repetition, but no between-group differences were found. The P3 was elicited by the first stimulus in each train only, and it was significantly larger in distractible than in non-distractible adolescents (p = 0.007) (Fig 8). The P3 response to the first stimulus of the first train did not differ between the two groups.

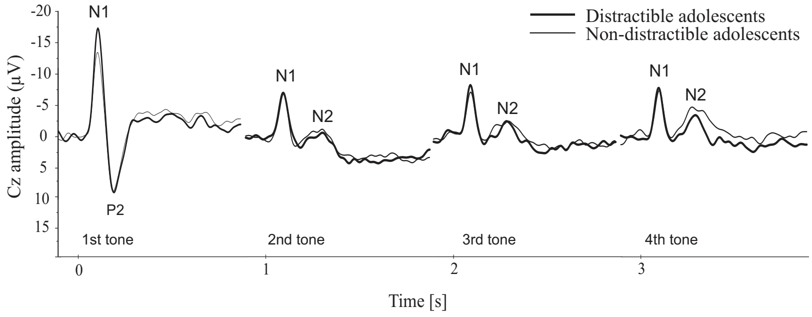

Figure 7: Responses to a train of four identical stimuli in distractible (thick line) and non-distractible (thin line) adolescents at CZ. The first tone in the train elicited a significantly larger N1 responses in the distractible than in the non-distractible adolescents, whereas the N1 responses to the 2nd, 3rd, and 4th were nearly identical. The N2 amplitude did not differ between the groups.

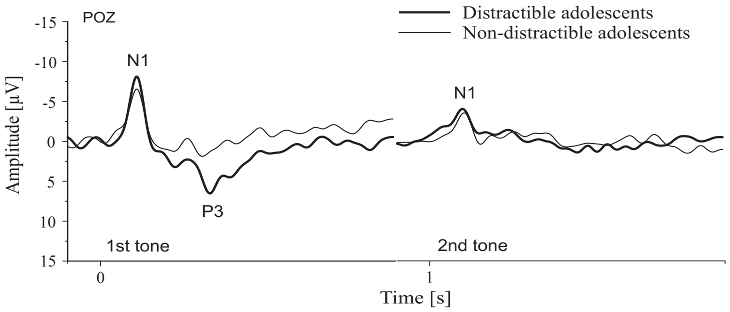

Figure 8: The first tone in the train elicited a parietal P3 wave that was significantly larger in amplitude in the distractible than in the non-distractible adolescent. The P3 was absent for the subsequent tones.

5.4 Time-on task effects on P3 response in distractible and non-distractible adolescent (Study IV)

We studied the P3 response to target stimuli at the beginning, in the middle, and at the end of a two-tone auditory oddball task in easily distractible and non-distractible adolescents. The P3 was evident at frontal, central and parietal electrode sites in distractible and non-distractible adolescents (Fig 9). Its topography was different between the two groups (group x anterior-posterior regions: F(2,60) = 8.060, p = 0.001): easily distractible adolescents showed enhanced frontal and reduced parietal P3 amplitude across the blocks relative to non-distractible adolescents (frontal electrode sites vs. the mean of central and parietal electrode sites, F(1,30) = 7.948, p = 0.008; central vs. parietal electrode sites F(1,30) = 8.401, p = 0.007). The P3 amplitude decreased between the 2nd and the 3rd block at all midline electrode sites. The change in P3 amplitude across the blocks was different for the two groups (group x block: F(2,60) = 3.478, p = 0.037). The interaction was due to a between-group difference in the P3 amplitude decrement between the second and the third block (2nd block vs. 3rd block, F(1,30) = 5.175, p = 0.03). This difference primarily reflects the greater drop in P3 amplitude from the 2nd block to the 3rd block in the distractible group.

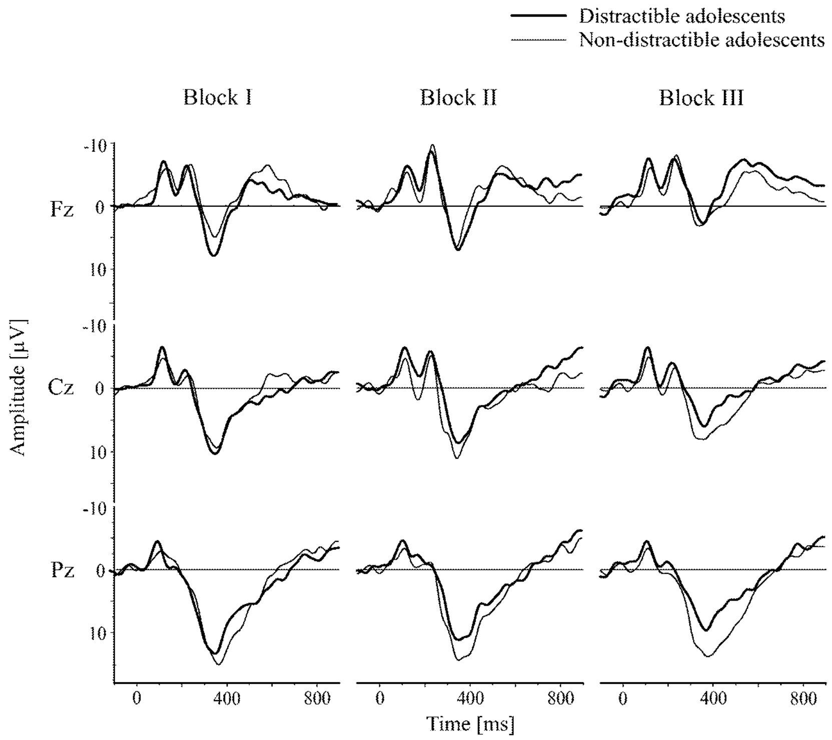

Figure 9: Grand-average ERP waveforms elicited by target stimuli at the beginning (block I), in the middle (block II) and at the end (block III) of an active auditory two-tone oddball task in distractible and non-distractible adolescents.

CHAPTER VI

DISCUSSION

6.1 ERP indicators of the orienting response

The OR is a reflexive attentional mechanism that is thought to facilitate information processing by enhancing perceptual sensitivity to environmental stimuli (Sokolov 1963; Öhman 1979). The OR is a collection of many different types of responses. Some are automatic such as a drop in skin resistance, some behavioural such as a change in reaction time due to task interference. Some responses are reflected as changes in the ERPs. In theory, the OR is an example of distraction, because it causes an involuntary attention switch towards the eliciting stimulus (Sokolov 1963). Of the autonomic, behavioural and electrophysiological responses of the OR, this study focused on the ERP correlates of novelty processing and distractibility in children and adolescents. The association of ERPs and the OR is well documented in the literature. In general, the N1, MMN and P3a are considered as ERP manifestations of the OR to novel or deviant stimuli (Escera et al 1998; Kok 2000). The N1 (Study III) and P3a (Studies I-IV) were used as indicators of the OR in this study.

The P3a is considered as an electrophysiological marker of the OR (Squires et al 1975b). The frontal lobes and hippocampal structures contribute to its generation (Knight 1996; Knight 1984), and these brain regions are known to be involved also in the OR (Fuster 1997). The association of the P3a generating process with the orienting response is further supported by its elicitation by highly deviant or novel stimuli (Courchesne et al 1975; Squires et al 1975; Knight and Scabini 1998) and also by the fact that behavioral RTs after stimuli that elicit P3a are prolonged (Escera et al 2000; Woods 1992). The habituation of the P3a i.e. the reduction of the frontal part of this component with stimulus recurrence is consistent with this hypothesis (Courchesne 1978a; Friedman et al 1998). Stimuli which engender an orienting response are typically accompanied by a phasic change in skin conductance as well as heart rate deceleration (Öhman 1979). Evidence that the P3a reflects orienting comes also from studies in which ERPs together with galvanic skin conductance and heart rate measures have been recorded to unexpected or novel event (Knight 1996; Lyytinen et al 1992).

In addition to P3a, the N1 component indexes central nervous system arousal (Näätänen and Picton 1987). Especially the non-specific part of the N1, which is usually recorded in response to auditory stimuli presented after silent intervals, is presumed to reflect activation of the orienting networks of the brain (Näätänen and Picton 1987). It is suggested to be generated in the frontal motor and premotor cortex under the influence of the reticular formation and the ventral lateral nucleus of the thalamus (Näätänen and Picton 1987). This transient arousal response appears to facilitate sensory and motor responses to the stimulus and also to shift the organism to a more efficient functional state. The long refractory period, the vigorous response when recovered, and the multimodal nature of this component support its interpretation as a transient arousal response.

6.2 Developmental aspects of processing of auditory novel events

In ERP studies of novelty processing, a commonly used experimental approach is the so-called novelty oddball paradigm. In this paradigm, three classes of stimuli are delivered: standard, high-probability events, low-probability deviant/target events, and novel events having the same probability as deviants/targets. In Studies I and II, a dichotic auditory novelty oddball paradigm was used. The major methodological difference between previous studies and this study series is that instead of using novel events that are equally probable to target/deviant events, we used a paradigm with very rare (2.4%) unique novel stimuli. The P3a component habituates rapidly, i.e. within the first few trials (Courchesne 1978a), and our paradigm was designed to minimise the possible habituation effects and thus to retain the "novelty" of the novel stimuli. The stimulus sequence was presented both in a passive (Study I) and an active conditions (Study II), and in both cases the novel tones elicited prominent P3a and Nc components in children and adults. Thus, even though the number of novel sounds was kept small, the basic morphology of the responses to novel tones is similar to those obtained in previous studies (Courchesne et al 1975; Escera et al 1998; Fabiani and Friedman 1995; Friedman et al 1998; Friedman et al 1992; Gumenyuk et al 2004; Gumenyuk et al 2001).

The ability to orient to biologically meaningful stimuli is important during development, because to acquire new information children must typically process many novel environmental events for which they have no previous representations (Luria 1973). With experience, representations of these kinds of stimuli would enable the child to avoid noxious or harmful environmental events and allow incorporation of these initially undefined and/or uncategorized environmental stimuli into appropriate semantic network. This kind of ability is critical for children so that they can classify these events into categories and detect truly new occurrences in the future (Luria 1973). ERP studies on novel-stimulus processing have shown that the ERPs elicited by novel tones, despite topographic differences, show no dramatic age-related changes (Ceponiene et al 2004; Courchesne 1978b; Cycowicz and Friedman 1997; Cycowicz et al 1996; Gumenyuk et al 2004; Gumenyuk et al 2001). Accordingly, in Study I the gross morphology of the ERPs elicited by novel stimuli was similar in children and adults, suggesting that processing of novel acoustic information is essentially similar across the age groups. However, the children's P3 components were more frontally oriented than those of adults, suggesting that children and adults use the brain's orienting networks differently. It is also possible that the adults were able to categorize the novel events even with only a few stimulus repetitions and this could have resulted in a posteriorly oriented P3 topography. Thus, unexpected stimuli retained their "novelty" and elicited the OR longer in children than in adults.

Study II aimed at studying how novel auditory information is processed in the attended and unattended channel. The OR (as indexed by P3a) appears not to be affected by the direction of attention. The novelty-elicited N2 was enhanced in the attended channel in adults, whereas in children, the amplitudes of the novelty-elicited N2 responses were smaller for the right-ear stimuli irrespective of the direction of attention. This asymmetry may be an index of brain laterality. The right hemisphere is crucial in attention and novel cognitive situations (Goldberg et al 1994), thus favoring the left ear input for novel unexpected tones. The children's N2 asymmetry was in some degree due to an overlapping slow positivity elicited by the novel tones to the right ear, suggesting that children allocate more resources to the processing of novel stimuli presented to the right ear than to the left ear. On the whole, the age-related differences found in this study suggest that adults are better able to maintain their attentional focus even in the presence of unexpected stimuli, whereas children show attention-independent automatic processing of such stimuli.

In Study I, the late negative components following P3a were larger in children than in adults. There is no clear consensus on the brain processes that generate these novelty-elicited negativities. Extensive cognitive assessment of novel stimuli (Courchesne 1990) and reorienting attention back to task after distraction (Schroger and Wolff 1998) have been proposed. Consequently, in Study I, the children's larger late negativities suggest either that their reorienting back to the current task after a distraction requires more and longer-lasting effort than in adults, or alternatively, attention paid to the surprising events is enhanced in children compared with adults (Courchesne 1990; Schroger and Wolff 1998). It is noteworthy that the previous studies supporting the reorienting theory of the negative component are based on the observation that in adults, the RON is absent in a passive condition (Schroger et al 2000; Schroger and Wolff 1998). However, in this study the RON was clearly evident in adults also in the passive condition, where the only task for the subjects was to watch a video. Since it is reasonable to think that the engagement to this task would not induce an effortful reorienting, our finding favors the theory of Courchesne (Courchesne 1990).

In summary, orienting to novel stimuli is a function known to be dependent on the frontal lobes (Daffner et al 2000b). The results of Studies I and II found differences between children and adults in activity associated with novel-stimulus processing, suggesting an age-related change in activity in the frontal part of the brain. This is consistent with findings showing that the structural maturation of the frontal cortex does not appear to be completed until late adolescence (Giedd 2004; Giedd et al 1999; Huttenlocher 1990).

6.3 Findings in distractible adolescents

In Study III, the easily distractible adolescents showed a large N1 potential in response to the first stimuli of the train when trains of identical tones were presented intermittently. Subsequent tones in the train elicited smaller N1 responses of about then same size in both attentive and inattentive adolescents. The N1 amplitude decrement between the first and the second stimulus presentation can be interpreted in terms of extinction of the non-specific, or orienting, part of the N1 after the first stimulus presentation (Näätänen 1992; Näätänen and Picton 1987). Since the distractible group produced significantly larger N1 potentials in response to the first stimulus but subsequent presentations of identical tones caused N1 responses of an equal size in both groups, the difference between the two groups may be in the strength of the OR-related activity.

In Study III, the adolescents also showed a small N2 from the 2nd stimulus onwards, but the amplitude of this component did not differ between the groups. Unlike N1, which habituates, the children's N2 to non-attended stimuli increases in amplitude with stimulus repetition. This dual behavior is suggested to reflect an automatic build-up of neuronal representations in developing networks (Karhu et al 1997). Since the N2 was equal in amplitude in distractible and non-distractible adolescents, the two groups seem to be equally able to form functional neuronal representations of such stimuli.

In Study III, the first stimulus in the train elicited a parietal P3 in both attentive and inattentive adolescents. It was concluded that this component is analogous to the P3a. The reason for its presence might be that even though the standard stimuli were ignored by the subjects in our study, the first stimulus of the train were perceptually salient enough to cause a momentary shift of attention towards the stimulus. This P3 to the first stimulus in the train was significantly larger in distractible than in non-distractible subjects, suggesting that the non-distractible adolescents were better able to screen out irrelevant stimuli from further processing resulting in reduced P3 amplitudes to unimportant stimuli, whereas the easily distractible adolescents allocate proportionately more attention to the irrelevant stimuli. This interpretation is in accordance with results of a previous study, in which it was found (using an auditory two-tone discrimination paradigm in 6-13-year-old children) that the non-target P3b component was globally increased in the ADHD group compared with the control group, suggesting more effortful processing of non-target stimuli in the ADHD subjects (Johnstone and Barry 1996).

In Study IV, the main finding was that the easily distractible adolescents showed an enhanced frontal and reduced parietal P3 amplitude across the blocks relative to the non-distractible adolescents, and that the usual decline in P3 amplitude at the end of the task was significantly larger in the distractible than in non-distractible adolescents. Previous ERP studies have shown that several neuropsychiatric disorders are characterized by small amplitude parietal P3 (Bauer and Hesselbrock 1999a; Bauer and Hesselbrock 1999b; Bauer and Hesselbrock 2003; Blackwood et al 1987; Iacono et al 2003). Study IV showed that altered P3 amplitudes can be seen in normal subjects who only show enhanced distractibility in neuropsychological tests. Thus, increased distractibility may at least partly account for the P3 amplitude decrement found in clinical disorders. The different topography of P3 between the two groups suggests differences in the strength by which the functionally different neural networks underlying the P3 are activated. The larger decline in P3 amplitude at the end of the task in distractible than in non-distractible adolescents may reflect between-group differences in the amount of resources allocated to the task with continued testing.

Since increased susceptibility to distraction is a symptom of several psychopathologic disorders, the results of this work may provide useful information about cognitive processes also in children and adolescents with attention, language, or learning disabilities. Up to now, the mechanisms of childhood and adolescence distractibility have been studied mostly in subjects with ADHD. The current theory of ADHD suggests that poor behavioral inhibition is the central impairment of the disorder, and that distractibility is only a consequence of the problems in self-regulation (Barkley

1997). Studies III and IV suggest, however, that the susceptibility to distraction in adolescence is characterized by an abnormally strong OR, indicating a deficit in the early selection of stimulus into conscious processing. This work also suggests that distractible adolescents allocate proportionately more attentional resources to the irrelevant stimuli as indexed by larger parietal P3 amplitude to the first stimulus of each train (Study III), and less to the relevant stimuli as indexed by their abnormally large decline in P3 amplitude at the end of the task (Study IV).

6.4 Distractibility and the orienting networks

The P3 is a measure of activation of multiple neocortical and limbic regions on relation to the allocation of voluntary and involuntary attention to a stimulus. Voluntary detection of an infrequent and task-relevant stimulus generates a large the P3b with a maximum over the parietal scalp sites, and involuntary orientation to an unexpected and novel stimulus generates a P3a with a frontocentral maximum (Knight and Scabini 1998). The frontal P3a reflects a passive shift of attention and is considered as an electrophysiological manifestation of the orienting response, whereas the posterior P3b is associated with stimulus evaluation processes. The P3a has been suggested to reflect the activity of a putative neuronal circuit that includes both anterior and posterior brain regions (Friedman et al 1993). In Study I, the children's novelty-elicited P3a component showed a frontal maximum, whereas in adults, the P3a was maximal at central electrode sites. This topographic difference suggests that children and adults use the frontal and posterior cerebral networks differently in the processing highly novel events. In Study IV, the distractible adolescents showed decreased parietal but increased frontal P3 to target stimuli compared with non-distractible subjects. In this study, the significantly shorter peak latency of P3 at Fz than at Pz suggests that the frontal P3 might be P3a (and not perhaps P3b). Therefore, Study IV suggests that the relatively enhanced frontal generation of P3 may be due to enhanced involuntary shifting of attention.

The human ERP results, in conjunction with neuropsychological observation and monkey single unit and metabolic data (Friedman and Goldman-Rakic 1994) support the notation that there is an interaction between prefrontal and posterior regions in the neural mechanisms responsible for voluntary and involuntary attention and working memory. The prefrontal cortex is essential for allocating attentional resources, especially under circumstances in which the behavioral response is not clearly defined in advance (Daffner et al 2003). The posterior parietal lobe may have a central role in the top-down control of attention (Corbetta et al 2000; Shulman et al 2001). Studies I and IV suggest that a defective interaction between these regions might predispose to distraction.

CHAPTER VII

SUMMARY AND GENERAL CONCLUSIONS

This study examined the neural mechanisms of novelty processing and distractibility in children and adolescents by means of ERPs. Given that attention processes in children are characterized by distractibility and less persistence, the differences between children and adults can bring insight not only to the development of attentional brain functions, but also to the functional basis of increased distractibility.

1. **Developmental aspects of novelty detection** (Studies I and II)

In the non-attended condition, the gross morphology of the ERPs elicited by complex, unique novel stimuli was similar in children and adults suggesting that processing of novel acoustic information is essentially similar across the age groups. However, the more frontally distributed P3 components and the larger late frontal negativities in children than in adults suggest an age-related change in activity in the frontal part of the brain. Also, in the attended condition, adults appear to be better able to selectively attend to the instructed ear and to maintain their attentional focus event in the presence of unexpected stimuli, whereas children show attention-independent automatic processing of such stimuli.

2. **Neural basis of increased distractibility in adolescence** (Studies III and IV)

Adolescence distractibility may be associated with deficits in early stages of information processing, probably already in the selection of stimuli into conscious processing. Also, distractible adolescents seem to allocate proportionately more attentional resources to irrelevant stimuli and less to the relevant stimuli than non-distractible adolescents. In the future, it might be beneficial to study to what extent the abnormalities in the attention-dependent processing of relevant stimuli are secondary to deficits in the preattentive processing of changes in the auditory stimulus environment.

3. **Distractibility and the orienting networks (**Studies I and IV)

Susceptibility to distraction may be related to the defective interaction of the cortical networks mediating voluntary and involuntary attention. The processing of unattended novel stimuli in children versus adults and the processing of target stimuli in distractible versus non-distractible adolescents show analogous changes in the responses between frontal and parietal recording sites. This suggests that susceptibility to distraction may be related to maturational or other defects in the interaction of the cortical networks that mediate voluntary and involuntary attention.

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