The Effects of Early Maternal Deprivation on Auditory Information Processing in Adult Wistar Rats

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Background: *There is now ample evidence that schizophrenia is due to an interaction between genetic and (early) environmental factors which disturbs normal development of the central nervous system and ultimately leads to the development of clinical symptoms. Recently, we showed that a single 24-hour period of maternal deprivation of rat pups at postnatal day 9 leads to a disturbance in prepulse inhibition, similar to what is seen in schizophrenia. The present set of experiments was designed to further characterize the information processing deficits of maternally deprived Wistar rats.*

Methods: *Wistar rats were deprived from their mother for 24 hours on postnatal day 9. At adult age, rats were tested in the acoustic startle paradigm for prepulse inhibition and startle habituation. Rats were also tested in the evoked potentials paradigm for auditory sensory gating.*

Results: *The results show that maternal deprivation led to a reduction in acoustic startle habituation and auditory sensory gating in adult rats. Moreover, maternal deprivation disrupted prepulse inhibition but only when the prepulses were given shortly (50–100 milliseconds) before the startle stimulus. At longer intervals (250–1000 milliseconds), no effect was seen.*

Conclusions: *The implications for the model and the development of disturbances in information processes are discussed.*

Key Words: Animal model, auditory sensory gating, acoustic startle habituation, prepulse inhibition, schizophrenia, neurodevelopment

In normal daily life, individuals are exposed to a large number of different external (and internal) stimuli. To adequately cope with these demands, a number of information processing mechanisms have emerged. These mechanisms have been conceptualized as filtering processes by a number of authors (Carr and Wale 1986; Treisman and Gelade 1980; Broadbent 1971). In general, these authors differentiate between two types of filters: 1) A fast (parallel) quantitative filter, generally referred to as sensory gating, and 2) a slower (serial) qualitative filtering mechanism, generally referred to as selective attention (Carr and Wale 1986).

Given its fundamental nature, it is not surprising that deficits in information processing can lead to strong disturbances in cognition and behavior. One of the most prominent examples of diseases in which information processing deficits occur is schizophrenia (Braff 1993; Carr and Wale 1986). In this severe psychiatric disease, disturbances in both sensory gating and selective attention have been described. Patients with schizophrenia have less sensorimotor gating, as measured with the prepulse inhibition paradigm (Braff et al 1978; Kumari et al 2000; Mackeprang et al 2002; Weike et al 2000), and a reduction in the speed of habituation of the acoustic startle response (Braff et al 1992). In addition, these patients also have shown less sensory gating, as measured with the P_{50} evoked potential paradigm (Adler et al 1982; Judd et al 1992; Freedman et al 1987). This latter paradigm is also referred to as auditory sensory gating.

These paradigms have the clear advantage that they can be studied in humans and animals with virtually identical techniques, thus offering the opportunity to study the neuronal basis, as well as the development of these information processing deficits (Ellenbroek and Cools 1995a, 2000a; Geyer and Markou 1995).

The plethora of clinical evidence that schizophrenia has a neurodevelopmental component (Weinberger 1996; Pilowsky et al 1993) has led to the development of novel animal models for schizophrenia, focusing specifically on the long-term consequences of early environmental manipulations. Thus, it has been shown that early postnatal lesions of the hippocampus (Lipska et al 1995; Le Pen and Moreau 2002) or of the dopaminergic system (Schwarzkopf et al 1992) and isolation rearing (Geyer et al 1993; Varty and Higgins 1995) disrupt prepulse inhibition. Much less is known with respect to the effects of such early manipulations on sensory gating and habituation. Isolation rearing was found to reduce sensory gating (Stevens et al 1997) but to leave startle habituation intact (Varty and Geyer 1998). Likewise, early lesions of the dopaminergic system did not affect sensory gating in adult rats (Stevens et al 1996).

Recently, we showed that a single 24-hour period of maternal deprivation (MD) early in life significantly reduced prepulse inhibition in postpubertal rats, an effect which could be temporarily reversed by antipsychotic treatment (Ellenbroek and Cools 2000b; Husum et al 2002; Ellenbroek et al 1998). We have subsequently shown that these maternally deprived animals also share other features with schizophrenic patients, such as an enhanced sensitivity to dopaminergic drugs and stress, as well as a reduction in latent inhibition (Ellenbroek and Cools 1995b, 2002a). Moreover, maternal deprivation seems to predominantly affect the hippocampal formation (Husum et al 2002; Roceri et al 2002), a neuronal structure often implicated in the neuropathology of schizophrenia (Weinberger 1999; Harrison 1999). All these data together have led to the hypothesis that the maternally deprived rat might represent an interesting animal model for specific aspects of schizophrenia.

The aim of the present study was to further characterize the behavioral consequences of early maternal deprivation. More specifically, we have investigated the effects on sensory and sensorimotor gating and startle habituation.

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Methods and Materials

Animals

Male and female (nulliparous) Wistar rats were obtained from the Central Animal Laboratory of the University of Nijmegen. The animals were housed in pairs of one male animal and one female animal in a standard Macrolon cage (26 × 42 × 15 cm) in a temperature-controlled room (22°C ± 2°C) on a standard 12 hours light/dark (light on at 7:00 AM) cycle. Food and water were available ad libitum. Two weeks later, the male animals were removed and the female animals were checked twice daily (8:00 AM and 5:00 PM) for delivery. The day of delivery was designated postnatal day (pnd) 0. Within 24 hours after birth, the litters were culled to 8 animals (6 male animals and 2 female animals). Maternal deprivation took place at pnd 9. The mothers were removed from the cage around 10:00 AM and placed in a single cage housed in the same room as the pups. The pups were weighed and left in the home cage at room temperature. In control litters, mothers were removed at pnd 9, pups were weighed, and mothers were returned immediately (within 3 minutes). At pnd 10 (24 hours later), the deprived pups were weighed again and the mothers placed back in the home cage. In the control litter, the mothers were again removed, the pups were weighed, and the mothers placed back in the cage. After this, the litters were left undisturbed, except for cleaning of the cage once a week until weaning (pnd 21), after which the male animals were housed in groups of 2 or 3 animals per cage. The female animals were not used in these experiments. All experiments were performed with independent (drug and experimentally naive) groups of rats between postnatal days 69 and 81. Rats from at least three different litters were used in each experiment.

Acoustic Startle Paradigm: Prepulse Inhibition and Habituation

In this paradigm, all rats were weighed before the experiment and placed in standard startle boxes of San Diego Instruments (San Diego, California), which were placed in a sound attenuated chamber. Each startle box consisted of a Plexiglas tube (diameter 8.2 cm, length 25 cm), in which the rats were individually placed. The tube was mounted on a plastic frame, under which a piezoelectric accelerometer was mounted, which recorded and transduced the motion of the tube. The resulting movement of the rat in the startle chamber was measured during 100 milliseconds after startle stimulus onset (sampling frequency 1 kHz), rectified, amplified, and fed into a computer which calculated the maximal response over the 100-millisecond period. The rats were placed into the chamber; they were allowed to habituate for a period of 5 minutes during which 70 dB(A) background white noise was present. After this habituation period, one of two different experiments was performed: prepulse inhibition or startle habituation.

Prepulse Inhibition. In the prepulse inhibition experiments, the 10 control and 10 maternally deprived rats were subjected to 5 startle trials and 25 prepulse inhibition trials. Although, in general, trials are presented 10 times instead of 5 times, we decided to reduce this to 5, since we had 5 different trial types (normally 2 or 3 types are used). Comparing the present data with those obtained in previous experiments (using 10 trials per trial type) showed that the variability was hardly increased (data not shown). The intertrial interval was between 10 seconds and 20 seconds and the total session lasted about 17 minutes. The startle trial (P120) consisted of a single 120 dB(A) white noise burst lasting 20 milliseconds. The prepulse inhibition trial (PP3) consisted of a prepulse (20-millisecond burst of white noise with intensities of 73 dB[A]), followed by a startle stimulus (120 dB[A], 20 milliseconds white noise). To test the influence of the interstimulus interval, the prestimulus was delivered 50, 100, 250, 500, or 1000 milliseconds before the startle stimulus. Each of these prestimulus-startle stimulus combinations was given 5 times (in total, 25).

Differences in basal startle amplitude (calculated as the mean response to the five startle stimuli) were analyzed by a one-way analysis of variance (ANOVA). Prepulse inhibition was calculated as 100* PP3/P120. The overall effect on prepulse inhibition was determined by a two-factor ANOVA, with the interstimulus intervals as repeated measures and condition (deprived vs. control) as between-group factor. Post hoc Student *t* tests were performed to detect the source of the statistical significance.

Startle Habituation. In a separate set of animals, startle habituation was assessed using the same acoustic startle boxes. After 5 minutes of habituation, 12 control and 9 maternally deprived animals were subjected to 50 startle trials (see above), with an intertrial interval varying between 10 seconds and 20 seconds. The data were analyzed in 10 blocks of 5 trials. Habituation was determined by 100* BLx/BL1, with BLx representing the mean of the five startle responses in block x and BL1 representing the mean of the first block of 5 startle responses. The overall difference was determined by a two-factor ANOVA with repeated measures for blocks and condition (deprived vs. control) as between-group factor. Post hoc Student *t* test was performed to detect the source of the statistical significance.

Auditory Sensory Gating

Ten control and 10 maternally deprived animals were equipped with tripolar cortical electroencephalogram (EEG) electrodes. Electroencephalogram electrodes were permanently implanted under pentobarbital anesthesia (60 mg/kg intraperitoneally [IP]) in the frontoparietal cortex and striate cortex area 17 with coordinates A 2.0, L 3.5, and A −6.0, L 4.0, respectively (Paxinos and Watson 1997). The ground electrode was placed in the cerebellum. Three screws and dental acrylic cement were applied to secure the electrodes to the skull surface. The animals were allowed to recover from surgery for 2 weeks.

Auditory sensory gating mechanisms were assessed in a conditioning-testing (C-T) paradigm by measuring the suppression of response to a 95-dB click test stimulus (duration of 1 millisecond) following an earlier identical conditioning stimulus at a .5-second interval. The intertrial interval was varied between 5 seconds and 10 seconds. On the 3 days before testing, the rats were handled daily, and 12 hours before testing they were connected to dummy EEG leads to habituate. The experiment was performed in freely moving animals. Before recording, animals were exposed to background white noise (70 dB) and stimuli for 2 hours to avoid interference of a habituation process on gating. Auditory evoked potentials (AEP) were recorded for 1 hour (462 trials) at a sample frequency of 1024 Hz with high pass filter set at 1 Hz, low pass set at 500 Hz, and a notch filter to reduce 50 Hz. The EEG was amplified, monitored, digitized, and stored for an off-line analysis using a WINDAQ system (KUN, Nijmegen, The Netherlands). Simultaneously, the behavior of the animals was observed through the window of the recording cage and scored on a separate channel. This was done to make a grand average AEP per rat based on trials in which the rat was quiet and awake only (passive wakefulness). The AEPs were averaged, taking into account prestimulus baseline values (100 milliseconds before the beginning of the stimulus). Because the distance between the speaker and the animal's head was about 1

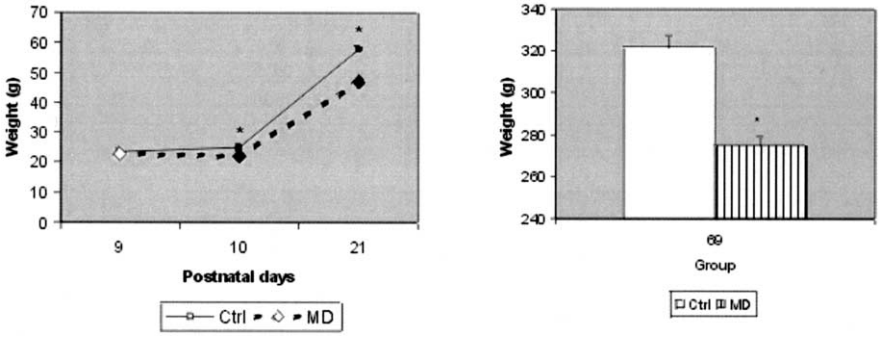

Figure 1. The effects of maternal deprivation on body weight (postnatal days 9, 10, and 21 on the left and 69 on the right). Deprivation was performed between days 9 and 10. Represented are the means ± SEM of 24 control (Ctrl) and 26 maternally deprived (MD) rats. Asterisk denotes a significant difference (post hoc analysis).

meter, the time axis of the AEP was adjusted by 2 milliseconds. Finally, grand average AEPs were calculated per group.

Several parameters were used to evaluate effects on auditory evoked potentials: peak-latency (in milliseconds) for the conditioning (first click) and test (second click) stimuli (CLAT and TLAT, respectively), and peak-peak amplitude (in μV) of the conditioning and test waveforms (CAMP and TAMP, respectively). Gating was calculated according to the following formula: CAMP − TAMP or (C − T). Smith et al (1994) consider that this C − T difference score is the most reliable P50-gating score for psychometric reasons. Data were analyzed with an ANOVA for both the individual C and T components, as well as for the C − T difference scores for the various components of the evoked potential.

Results

Body Weight

Figure 1 shows the effects of maternal deprivation on body weight. The data clearly show that maternal deprivation led to a significant reduction in body weight, which lasted at least until the first day of testing (pnd 69). Analysis of variance confirmed that there was a significant effect of days [$F_{(3,144)} = 6130$, $p < .001$] and of maternal deprivation [$F_{(1,48)} = 75.2$, $p < .001$], as well as a significant interaction [$F_{(3,144)} = 40.2$, $p < .001$]. Post hoc analysis showed that rats of the MD group were significantly smaller at postnatal days 10, 21, and 69, but not at pnd 9.

Prepulse Inhibition

The two groups did not differ in basal startle amplitude [MD, $n = 10$: 1173 ± 207; Control, $n = 8$: 1015 ± 132, $F_{(1,16)} = .4$, $p > .5$]. The effects on prepulse inhibition are depicted in Figure 2. The ANOVA showed a significant interstimulus interval effect [$F_{(4,64)} = 17.5$, $p < .001$], no significant effect of maternal deprivation [$F_{(1,16)} = 2.2$, $p = .16$], but a significant treatment × interstimulus interaction [$F_{(4,64)} = 2.8$, $p < .04$]. Post hoc Student t test analysis showed that the MD groups had significantly reduced prepulse inhibition at 50 and 100 millisecond interstimulus intervals. At larger intervals, the two groups did not differ.

Startle Habituation

The effects of maternal deprivation on startle habituation are shown in Figure 3. Again, there was no significant difference in basal startle amplitude (calculated as the mean of the first five startle stimuli): MD ($n = 9$): 742.3 ± 92.1; Control ($n = 12$): 849.3 ± 105.1; $F_{(1,19)} = .5$; $p > .45$. Both groups showed a clear habituation of the startle response on repeated stimulus presentation. This was confirmed by the ANOVA for blocks [$F_{(9,171)} = 29.4$, $p < .001$] and for condition. More interestingly, there was a significant difference between the two groups [$F_{(1,19)} = 4.6$, $p < .05$], as well as a significant maternal deprivation * block interaction [$F_{(9,171)} = 3.7$, $p < .001$]. Figure 3 shows that startle habituation was diminished in maternally deprived rats. Post hoc Student t tests showed that the two groups differed significantly in all blocks except 1, 5, 8, and 9.

Auditory Sensory Gating

One of the maternally deprived animals had to be discarded because a reliable EEG signal could not be detected. As a consequence, there were 10 rats in the control group and 9 rats in the maternally deprived group. The (repeated) presentation of acoustic stimuli produced two consecutive evoked potentials, each of which had three clearly distinguishable components (Figure 4): a positive wave with maximal amplitude around 13 milliseconds after stimulus presentation (P_1), a negative wave with a maximal amplitude around 35 milliseconds (N_1), and a second positive wave with maximal amplitude around 60 milliseconds (P_2). There were no effects of maternal deprivation on the latency of each of these three components (data not shown). Analysis of variance showed a significant reduction in CAMP of both the N_1 component [$F_{(1,17)} = 17.05$, $p < .001$] and of the P_2 component [$F_{(1,17)} = 15.82$, $p < .001$] in MD rats (Figure 4A). Moreover, gating of both the N_1 [$F_{(1,17)} = 7.13$, $p < .02$] and of the P_2 [$F_{(1,17)} = 11.32$, $p < .005$] was reduced in the animals maternally deprived at postnatal day 9 (Figure 4B).

Discussion

The present article shows that early maternal deprivation of Wistar rats led to a general disturbance in auditory information processing, as evidenced by a reduction in prepulse inhibition, in startle habituation, and in auditory sensory gating. Interestingly, all these aspects of auditory information processing are also

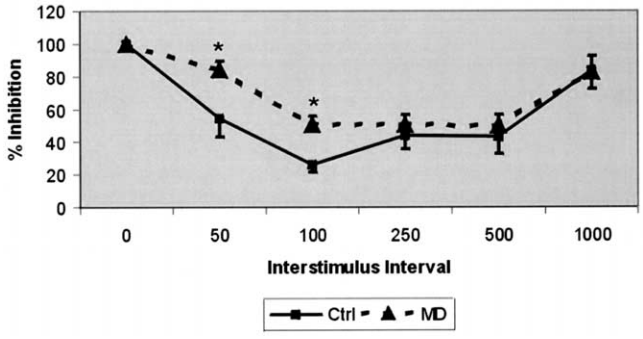

Figure 2. The effects of maternal deprivation on startle amplitude as a function of interstimulus interval between the prestimulus and the startle stimulus (x axis). The degree of prepulse inhibition is represented on the y axis (see Methods and Materials for calculation). Represented are the means ± SEM of 10 control (Ctrl) and 10 maternally deprived (MD) rats. Asterisk denotes a significant difference (post hoc analysis).

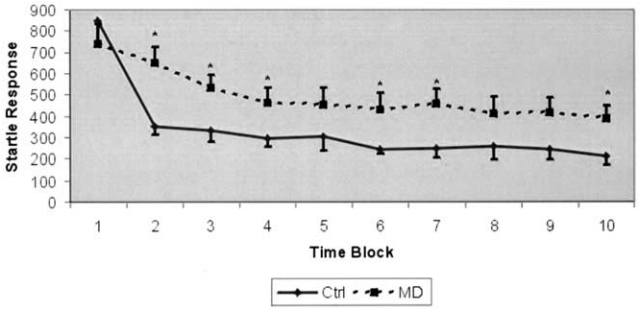

Figure 3. The effects of maternal deprivation on startle habituation, as a function of blocks of five trials (x axis). The degree of habituation is represented on the y axis (see Methods and Materials for calculation). Represented are the means ± SEM of 24 control (Ctrl) and 26 maternally deprived (MD) rats. Asterisk denotes a significant difference (post hoc analysis).

disrupted in patients suffering from schizophrenia. Before discussing the possible implications of these data, it is important to look at the data in more detail.

A single 24-hour episode of maternal deprivation in Wistar rats led to a significant reduction in prepulse inhibition. This is in agreement with previous data from our laboratory (Ellenbroek et al 1998; Husum et al 2002). Although this could not be confirmed by another group, this may be due to differences in methodology or in rats (Lehmann et al 2000). Indeed, we have recently shown that this effect of maternal deprivation strongly depends on the strain of rats used. Thus, maternal deprivation in Wistar rats reduced prepulse inhibition without affecting basal startle amplitude. Maternal deprivation in Lewis rats, on the other hand, reduced basal startle amplitude but did not affect prepulse inhibition, whereas in Fischer 344 rats neither basal startle amplitude nor prepulse inhibition was affected (Ellenbroek and Cools 2000b). Moreover, the long-term consequences of early maternal deprivation also depend on the postdeprivational period (Ellenbroek and Cools 2002b). A new finding in the present article is that prepulse inhibition was only disturbed at the shorter interstimulus intervals. Thus, the maternally deprived group differed from the control group only when the interval between prepulse and startle stimulus was 50 or 100 milliseconds. It is not clear whether this is due to the fact that prepulse inhibition is maximal at these short intervals or whether there is a more fundamental difference between short-term and long-term intervals. Only very few studies have looked at the effects of treatments on interstimulus intervals. In one study, the noncompetitive N-methyl-D-aspartate (NMDA) antagonist ketamine was found to disrupt prepulse inhibition only at specific intervals (Mansbach and Geyer 1991). Thus, prepulse inhibition was disrupted at interstimulus intervals of 60 to 500 milliseconds but not at 30 or 2000 milliseconds. This selective effect was recently confirmed with another noncompetitive NMDA antagonist phencyclidine (Jones and Shannon 2000). Mansbach and Geyer (1991) argue that a prepulse can either facilitate or inhibit the startle response and that the ultimate effect depends on the balance between the two influences. The authors propose a three-stage temporal course: a very short facilitatory effect that rapidly decays, a short-term inhibitory effect, and a longer facilitatory effect, the latter occurring at very long latencies (i.e., 2000 milliseconds or more). According to this model, noncompetitive NMDA antagonists primarily enhance the facilitatory effect without affecting the inhibitory effect. In view of this model, one might speculate that the effects of maternal deprivation are limited to an enhancement of prepulse facilitation, similar to the effects of ketamine (Mansbach and Geyer 1991). In this respect, it is interesting to note that we recently obtained evidence that maternally deprived rats are more susceptible to ketamine than control rats (BAE and ARC; Ellenbroek and Cools, unpublished data). In contrast to ketamine, apomorphine appears to disrupt prepulse inhibition at all interstimulus intensities (Jones and Shannon 2000).

Apart from the disruption of prepulse inhibition, maternal deprivation also led to a reduction in startle habituation (Figure 3). Pharmacological experiments have shown that both NMDA and serotonin (5-HT) receptors play an important role in startle habituation. Thus, NMDA antagonists such as phencyclidine (Geyer et al 1984), serotonin reuptake inhibitors such as fluoxetine (Geyer and Tapson 1988), and serotonin agonists such as Lysergic Acid Diethylamide (LSD) (Geyer et al 1978) can reduce startle habituation. As discussed above, there is evidence that maternal deprivation may alter the glutamate neurotransmission. With respect to serotonin, less is known; however, there is evidence that early environmental manipulation may alter serotonergic function. Thus, short-term handling (i.e., removing the litter from the mother for 15 minutes per day for the first 2 weeks of life) enhances 5-HT turnover (Meaney et al 1994). Maternal deprivation also alters serotonin receptor levels; however, the results are somewhat conflicting, since both increases (Sibug et al 2001) and decreases (Vazquez et al 2002) in messenger RNA (mRNA) for 5-HT_{1A} receptor in the CA_1 area have been described. In addition, an increase in mRNA for 5-HT_{1B} receptors has been described (Vazquez et al 2002). Again, differences in methodology and strains may underlie these differences. It therefore remains to be established whether alterations in serotonin are also induced by our deprivation method.

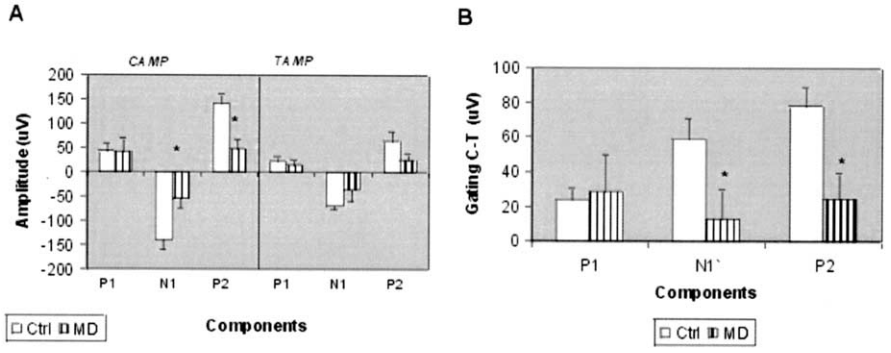

Figure 4. The effects of maternal deprivation on auditory sensory gating. **(A)** The individual components of the first (CAMP) and second evoked potential (TAMP). **(B)** The degree of gating (as measured by the subtraction of the amplitude of the second wave from the corresponding first wave, see Methods and Materials). Represented are the means ± SEM of 9 control (Ctrl) and 7 maternally deprived (MD) rats. Asterisk denotes a significant difference between groups (analysis of variance [ANOVA]).

An alternative method of measuring auditory information processing is through the use of auditory evoked potentials. Using the electrode placements described in Methods and Materials, we obtained an evoked potential with three clearly distinguishable components, two positive waves (around 13 and 60 milliseconds after stimulus presentation) and one negative wave (with a maximal response around 35 milliseconds) (van Luijtelaar et al 1998). All three components showed clear signs of gating, implying that the amplitude of the second potential was smaller than the amplitude of the first potential. To measure gating, we used a subtraction method (i.e., CAMP − TAMP) rather than a ratio method, since this gives a more reliable measurement of gating (Smith et al 1994). The data clearly showed that maternal deprivation reduced gating. This was most prominently seen in the N_1 component, although reduced gating of the P_2 component was also observed. Analysis of the ratios of CAMP/TAMP led to similar conclusions as the subtraction CAMP − TAMP method (data not shown). The effects of maternal deprivation on gating seem to be primarily due to a reduction of the amplitudes of the first evoked potential (CAMP) (Figure 4A). Although this may be somewhat surprising, it is a common pattern in pharmacological studies of sensory gating. For instance, amphetamine reduces sensory gating (as measured by the TAMP/CAMP ratio) by specifically decreasing the amplitude of the first wave (Stevens et al 1991, 1995; de Bruin et al 1999; Adler et al 1986). Likewise, systemic application of phencyclidine (Adler et al 1986) or cocaine (Boutros et al 1994) or local application of quinpirole into the nucleus accumbens (de Bruin et al 2001) reduced sensory gating by selectively reducing CAMP. In addition, several other manipulations that reduce sensory gating, including kainic acid lesions of the hippocampus (Stevens et al 1998) and isolation rearing (Stevens et al 1997) predominantly affect the amplitude of the evoked potential to the first stimulus.

Although it has been argued that prepulse inhibition and auditory sensory gating assess similar (if not identical) aspects of information processing, recent evidence shows that there are clearly differences. Thus, there is only a very weak correlation between the degree of prepulse inhibition and the degree of auditory sensory gating among individual Wistar rats (Ellenbroek et al 1999), as well as in healthy human volunteers (Schwarzkopf et al 1993; Oranje et al 1999). Likewise, early postnatal lesions of the dopaminergic cells with 6-hydroxydopamine (6-OHDA) decreases prepulse inhibition (Schwarzkopf et al 1992) without affecting auditory sensory gating (Stevens et al 1996). In a similar vein, we have recently found that ketamine disrupts prepulse inhibition without affecting auditory sensory gating (de Bruin et al 1999). Finally, one of the most convincing pieces of evidence that prepulse inhibition and auditory sensory gating are mediated via different neurobiological substrates comes from the effects of the serotonergic agonist DOI ([±±]-2,5-dimethoxy-4-iodoamphetamine). Whereas DOI significantly reduces prepulse inhibition (Sipes and Geyer 1994), it enhances auditory sensory gating (Johnson et al 1998). Thus, all these data clearly indicate that prepulse inhibition and auditory sensory gating measure different aspects of auditory information processing. Therefore, the current finding that both are disturbed in maternally deprived Wistar rats may be of high relevance for schizophrenia, since in this condition both aspects of information processing are disturbed. In this respect, it is of interest to note that isolation rearing, which is often considered one of the most important environmental models for schizophrenia (Ellenbroek and Cools 2002a), disrupts both prepulse inhibition (Geyer et al 1993) and sensory gating (Stevens et al 1997).

Overall, the present data indicate that maternal deprivation produces deficits in auditory information processing. Given the stressful nature of the deprivation, we might consider this an animal model of posttraumatic stress disorder (PTSD), especially as some papers have described deficits in prepulse inhibition (Grillon et al 1996) and P_{50} (Gillette et al 1997) in these patients; however, there are several arguments against this relationship. First of all, from a theoretical point of view, it is important to remember that in the model the stressful life event is given at a very early stage of development (comparable to the period around birth in humans). Second, the deficit in prepulse inhibition in patients with PTSD could not be replicated by others (Braff et al 2001). Third, as mentioned above, the P_{50} gating deficit in PTSD patients is not accompanied by a reduction in the amplitude of the first wave (Neylan et al 1999), as was clearly observed in the maternally deprived rats (Figure 4). Finally, and probably most importantly, PTSD is accompanied by a strong increase in startle amplitude, which has never been observed in our maternally deprived rats (Ellenbroek et al 1998; Ellenbroek and Cools 2000b; Husum et al 2002). If any significant effect was observed, maternal deprivation reduced baseline startle amplitude.

When reviewing the present data, it seems that maternal deprivation induced alterations which also occur in patients suffering from schizophrenia: a decreased prepulse inhibition (Braff et al 1978), a decreased auditory sensory gating (Adler et al 1982), and a retardation in startle habituation (Geyer and Braff 1982). Moreover, a closer examination of the present results suggests that the similarity is even more pronounced. Thus, whereas in patients prepulse inhibition is only disturbed at an interstimulus interval of 60 and 120 milliseconds but not at longer intervals, we found a similar time dependency in the present article. Moreover, in the auditory sensory gating paradigm in humans, the schizophrenic deficit in gating is primarily due to a decrease in the amplitude of the first wave (Waldo et al 1988; Adler et al 1982; Boutros et al 1993), which is similar to our finding. Interestingly, this pattern differs from manic patients (Franks et al 1983), from patients suffering from posttraumatic stress disorder (Neylan et al 1999), and from relatives of schizophrenic patients (Waldo et al 1988) with a sensory gating deficit in which the amplitude of the first P_{50} wave is not reduced.

In addition to the data found in the present article, other similarities between the maternally deprived rat and the schizophrenic patient have been reported. Both maternally deprived rats (Ellenbroek and Cools 1995b; Rots et al 1996; Zimmerberg and Shartrand 1992) and schizophrenic patients (Lieberman et al 1987; Muller-Spahn et al 1998) show a hypersensitivity to dopamimetics such as amphetamine or apomorphine. Likewise, maternally deprived rats (Rots et al 1996; Penke et al 2001) and schizophrenic patients (Lammers et al 1995; Altamura et al 1999) have increased levels of adrenocorticotropic hormone (ACTH) and corticosterone, as well as an increased response to stress. Finally, we have shown that maternally deprived rats (Ellenbroek and Cools 1995b) have a reduced latent inhibition, as has also been reported for schizophrenic patients (Baruch et al 1988; Gray et al 1995); however, the question of whether latent inhibition is disturbed in schizophrenic patients is still controversial. Thus, whereas the initial reports (Baruch et al 1988; Gray et al 1995) showed that latent inhibition was disturbed in the early stages of the illness, this could not be confirmed by others (Swerdlow et al 1996). Recently, it was even suggested that the disturbance in schizophrenic patients might be a medication artifact, since patients on haloperidol but not medication-free patients showed an abnormal latent inhibition (Williams et al 1998).

At present, it is unclear how the long-term effects of maternal deprivation develop. Since the acute effect of maternal deprivation is an increase in both basal and stress-induced levels of ACTH and corticosterone (Stanton et al 1988), it is likely that alterations in the hypothalamic-pituitary-adrenal (HPA) axis precede other changes. Indeed, we have been able to show that the disturbances in prepulse inhibition (Ellenbroek et al 1998), as well as the reductions in hippocampal mRNA levels of brain-derived neurotrophic factor and NMDA subunits (Roceri et al 2002), do not occur until after puberty, which resembles the occurrence of overt clinical symptoms in schizophrenic patients (Hafner et al 1993).

However, it is important to realize that maternal deprivation not only deprived the pups from their mother but also the mother from their pups. Thus, alterations in maternal behavior induced by the deprivation could also play an important role in the long-term effects. It has indeed been suggested that the long-term effects of handling (i.e., short-term deprivation) may be due to the increase in maternal care following reunion of mother and puppies (Meaney et al 1994). Since many of the effects of handling seem to be opposite to the effects of maternal deprivation, it is tempting to suggest that due to the long-term maternal deprivation, the maternal care is significantly reduced. Although we have, at present, no direct data to support this notion, it is interesting to note that the growth curves of control and maternally deprived litters do not run in parallel after reunion (Figure 1). In fact, whereas the control rats grow about 140% from pnd 10 to pnd 21, the deprived animals grow only 110% in the same time. This strongly suggests that the postdeprivation period is of critical importance. In agreement with this, we have recently found that cross-fostering immediately after the deprivation reduces the prepulse inhibition deficit in adulthood. Obviously, more experiments with direct observations of the maternal behavior are necessary to pinpoint the exact cause of the disturbance in development between maternally deprived and control rats.

In summary, the present article shows that a single 24-hour period of maternal deprivation early in life leads to alterations in the auditory information processing strongly reminiscent of schizophrenia. This may, therefore, represent an interesting model to study the basic mechanisms involved in the development of information processing, as well as investigating the possible disturbances induced by an early life event. Given the relation between early life events and the development of schizophrenia (Walker and Diforio 1997), this model may also contribute to our knowledge of the neurodevelopmental disturbances seen in schizophrenic patients.

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