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Prenatal Stress Changes Learning Strategies in Adulthood

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ABSTRACT: It is well known that stressful experiences may shape hippocampus-dependent learning and memory processes. However, although most studies focused on the impact of stress at the time of learning or memory testing, very little is known about how stress during critical periods of brain development affects learning and memory later in life. In this study, we asked whether prenatal stress exposure may influence the engagement of hippocampus-dependent spatial learning strategies and caudate nucleus-dependent response learning strategies in later life. To this end, we tested healthy participants whose mothers had experienced major negative life events during their pregnancy in a virtual navigation task that can be solved by spatial and response strategies. We found that young adults with prenatal stress used rigid response learning strategies more often than flexible spatial learning strategies compared with participants whose mothers did not experience major negative life events during pregnancy. Individual differences in acute or chronic stress do not account for these findings. Our data suggest that the engagement of hippocampal and nonhippocampal learning strategies may be influenced by stress very early in life. © **2012 Wiley Periodicals, Inc.**

KEY WORDS: prenatal stress; stress; cortisol; learning; navigation; multiple memory systems; hippocampus; caudate nucleus

INTRODUCTION

Stress is very common in today's modern societies. We all experience stress, in varying degrees and forms, every day. The effects of stress are manifold. Stress affects our health and well-being, our emotions, and our cognitions. The effects of stress on hippocampus-dependent learning and memory processes are particularly well documented. Short periods of stress may enhance or impair episodic or spatial memory, depending on whether it is experienced within or out of the learning context (Joëls et al., 2006; Schwabe et al., in press). Prolonged or repeated stress, however, has mainly detrimental effects on memory (Luine et al., 1994; Conrad et al., 1996; Wolf, 2008).

Over the past several years, research has revealed that acute or chronic stress influences not only how much we learn and remember but also how we learn, i.e., which strategies we use during learning [for a review, see (Schwabe et al., 2010b)]. Many tasks can be solved in different ways. For example, navigation tasks can usually be solved by a spatial strategy that makes use of the relation between multiple landmarks in the environment to create a "cognitive map" (O'Keefe and Nadel, 1978) or by a response strategy that associates a response with a single stimulus or a series of turns from an initial position (O'Keefe and Nadel, 1978; Packard et al., 1989). These strategies are supported by distinct brain structures: the spatial strategy is dependent on the hippocampus and the response strategy on the caudate nucleus (Kesner et al., 1993; McDonald and White, 1993; White and McDonald, 2002; Iaria et al., 2003). Moreover, these strategies differ in the flexibility of the acquired knowledge. Spatial strategies are associated with the acquisition of flexible knowledge that can be transferred to novel situations, whereas response strategies are rather rigid and inflexible (Mishkin and Petri, 1984; Reber et al., 1996). Both acute and chronic stress promote the engagement of simple but rigid response strategies, at the expense of flexible but cognitively demanding spatial strategies (Kim et al., 2001; Packard and Wingard, 2004; Schwabe et al., 2007, 2008, 2010a).

Although the vast majority of the studies on stress and memory focused on how acute or chronic stress during adulthood affects hippocampus-dependent memory, learning and memory may already be shaped by stress experiences made at a much earlier stage of life, even before birth. If mothers experience stress during pregnancy, glucocorticoids (cortisol in humans) and other hormones that are released in response to stress may influence the development of brain areas that are critically involved in memory processes, such as the hippocampus, in the fetus (Lupien et al., 2009). Indeed, rodent studies showed that the exposure to prenatal stress may lead to reduced hippocampal neurogenesis and impaired hippocampus-based memory processes in later life (Lemaire et al., 2000; Yang et al., 2006). In line with these findings, adult offspring of rat dams who consumed ethanol during pregnancy showed a predominant use of response learning strategies in a water maze task that could be solved with the two strategies (i.e., hippocampus-dependent spatial and caudate-dependent response strategies) compared with control rats (Sutherland et al., 2000).

Human studies on the impact of prenatal stress experiences on learning and memory are largely missing. Two studies indicated that children whose moth-

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ers were exposed to major stressors during pregnancy had poorer general intellectual and language abilities (Laplante et al., 2004; Niederhofer and Reiter, 2004). Moreover, one recent study suggested that prenatal stress may impair working memory in adulthood (Entringer et al., 2009a). However, whether prenatal stress exposure may affect hippocampus-dependent memory or the engagement of different (hippocampal and nonhippocampal) learning strategies in humans has not been investigated yet.

Thus, the goal of this experiment was to examine whether and how prenatal stress influences memory processes and in particular the engagement of different learning strategies in later life in humans. Because retrospective stress ratings are often unreliable, particularly after several decades, we used a rather conservative strategy to operationalize prenatal stress and defined it as the presence of major negative life events that occurred to the mother during her pregnancy (Entringer et al., 2009a,b, 2011). Our participants performed a learning task that was explicitly designed to allow the use of both spatial and response learning strategies. Previous studies that used this task showed that participants spontaneously adopt one of these two strategies and that the use of spatial and response strategies is associated with activity and gray matter of the hippocampus and the caudate nucleus, respectively (Iaria et al., 2003; Bohbot et al., 2007). To exclude the possibility that learning is affected by individual variations in acute or chronic stress levels, we included subjective and physiological measures of acute and chronic stress as control variables. We predicted that prenatal stress experiences would impede hippocampus-based spatial learning and thus promote the use of rather rigid response strategies.

MATERIALS AND METHODS

Participants

Sixty Bochum University students [24 women and 36 men; age: M = 24.47 yr and standard errors of the mean (SEM) = 0.42 yr] were paid 12€ per hour for participating in this experiment. Participation was limited to those between 18 and 32 yr of age, without medication intake, and with no reported history of any psychiatric or neurological disorders. All participants provided written informed consent in a manner approved by the local ethics committee.

Prenatal Stress Assessment

Prenatal stress exposure was assessed by means of a semi-structured questionnaire that was used in previous studies to measure the occurrence of major negative life events during pregnancy (Entringer et al., 2009a,b, 2011). This questionnaire lists a number of events that are considered highly stressful across individuals (e.g., sudden death of a beloved one, loss of primary residence, breakup or divorce, and severe illness). Moreover, because prenatal stress may be associated with perinatal risk factors and increased stress levels during the first year of life, the questionnaire also assessed whether there were any problems during birth (requiring, for example, an incubator or an oxygen tent) or any adverse conditions during childhood (e.g., death of father or mother, massive financial problems, and separation from a parent). Participants were asked to complete this questionnaire with their mothers, at home. In retrospect, the detailedness of the given answers suggested that participants indeed adhered to the instructions. For example, one participant reported that his father had died 2 months before the participant was born.

Control Variables: Acute and Chronic Stress

Because acute and chronic stress, as well as elevations in basal cortisol levels, may influence the engagement of different learning strategies (Schwabe et al., 2007, 2008; Bohbot et al., 2011), we took subjective and physiological measures to control for these influences. Participants completed a German mood questionnaire [MDBF (Steyer et al., 1994)] that measures subjective feeling on three dimensions (elevated vs. depressed mood, wakefulness vs. sleepiness, and calmness vs. restlessness) before the learning task. In addition, participants gave a saliva sample (with a Salivette® collection device) from which we analyzed the concentration of the stress hormone cortisol with an immunoassay.

Moreover, to control for a potential influence of chronic stress, participants completed a standardized chronic stress questionnaire [Trier Inventory for Chronic Stress (Schulz and Schlotz, 1999)] and were asked to collect three saliva samples at home immediately after awakening in the morning as well as 30 and 60 min after awakening. These saliva samples allow the assessment of the cortisol awakening response, a strong rise of cortisol in response to awakening (Pruessner et al., 1997). An elevated cortisol awakening response has been repeatedly associated with chronic stress [for a review, see (Chida and Steptoe, 2009)].

Learning Task and Procedure

After participants had collected the saliva sample and completed the mood questionnaire, they were presented a virtual radial maze on a computer screen, the four-on-eight virtual maze (4/8 VM) (Fig. 1a). This maze was made to resemble the basic structure of the radial maze used for rodents (Olton and Samuelson, 1976) and has been used in previous studies (Iaria et al., 2003; Bohbot et al., 2007). Eight arms originated from a central platform and each terminated in a staircase leading to a lowered chamber. The VM was surrounded by two proximal cues (tree and rock) and two distal cues (mountains and another tree). Participants could move through the maze by using the forward, left, and right keys on a keyboard. Before testing began, participants were allowed to familiarize themselves with the keys in a virtual practice room containing a radial maze without staircases or surrounding landscape. Once

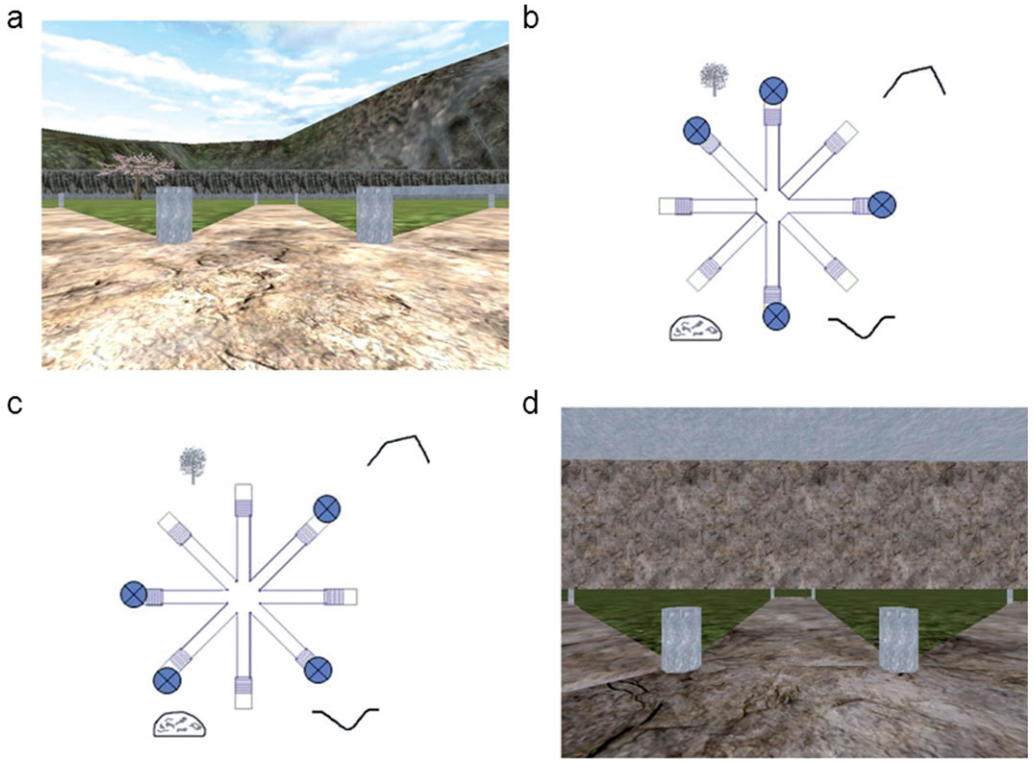

FIGURE 1. Illustration of the learning task. Participants moved though a virtual eight-arm maze surrounded by landmarks and a landscape. (a and b) Screenshot from and scheme of the first part of a trial in which participants retrieved objects (as indicated by the x in the scheme) from the ends of the open arms. (c) In the second part of a trial, all arms were open but objects were only present in the arms that were not accessible in part one. (d) Screenshot from the second part of the probe trial in which all spatial cues were removed. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

participants were able to move efficiently with the keys, the learning task started.

All testing took place on the same day in one continuous session, for a total duration of about 25 min. Participants were presented three training trials, each consisting of two parts. In the first part, four of the eight radial maze arms were open and objects (small golden statues) were placed in the lowered chambers at the ends of these arms; the other four arms were blocked (Fig. 1b). In the second part, all arms were open but objects were only present in those arms that were blocked in the first part (Fig. 1c). Participants were instructed to retrieve the objects in the open arms in part one and to avoid these arms in part two (in which they should retrieve the objects from the previously blocked arms). Entering an arm that had been visited before (either in the same part or in the previous part) was counted as an error. It should be noted that the presence or absence of the objects could not be seen from the central platform; they could only be seen upon entry into a given arm. The sequence of accessible and blocked arms was the same in training trials 1 and 3; in trial 2, a different sequence was used. If participants made an error in the second part of the third trial, they were given up to two additional training trials.

Importantly, participants could use spatial or response strategies to learn this task. The used learning strategy was revealed in a probe trial that was presented immediately after the last training trial. The first part of the probe trial was identical to the first part of the first and third training trial. In the second part of the probe trial, however, all visual cues (landmarks and landscape) were removed (Fig. 1d). If participants were using a spatial strategy, removing the visual cues in the second part of the probe trial should impair performance. However, if participants were using a response strategy, their performance should be less affected by the changes in the probe trial.

After completing the learning task, participants were instructed to draw a map of the virtual maze including all landmarks (participants could reach a maximum score of 8 for a correct and complete map, one point for each of the landmarks and its correct location). Afterward, participants were asked to report how they solved the learning task. These reports were analyzed by two independent raters who categorized participants based on their reports as response or spatial learners. Participants were categorized as response learners if they associated the arms with numbers or letters or if they counted the arms from a single start point that acted as the stimulus. The response strategy can be egocentric when a participant is using his/her own position as a starting position (e.g., an egocentric response strategy can be done in the dark or in a virtual environment devoid of landmarks). Note, however, that the response strategy is not egocentric when an external landmark is used as a stimulus (e.g., counting a series of

TABLE 1.

Sample Characteristics

	Prenatal stress group (n = 19)	Comparison group (n = 41)
Number of major negative events during intrauterine life	2.74 (0.34)	None
Perinatal problems	10.5%	19.5%
Adverse conditions during childhood	1.26 (0.23)	0.73 (0.19)
Education of the mother		
High school	95%	93%
College graduate	28%	25%
Current		
Age	25.56 (0.81)	23.96 (0.46)
Sex ratio (women/men)	10/9	14/27
Body mass index (kg/m^2)	22.72 (0.77)	22.79 (0.36)
Education: high school	100%	100%
Current or chronic diseases	None	None
Acute stress parameters before testing		
Salivary cortisol (nmol/l)	8.06 (0.89)	7.73 (0.60)
Mood scale: calmness vs. restlessness	29.06 (0.96)	31.04 (0.95)
Mood scale: sleepiness vs. wakefulness	28.42 (1.37)	29.34 (1.05)
Mood scale: depressed vs. elevated mood	31.32 (1.24)	32.93 (0.84)
Chronic stress parameters		
Salivary cortisol directly after awakening	14.83 (1.29)	15.58 (1.20)
Salivary cortisol 30 min after awakening	24.24 (1.22)	23.45 (1.16)
Salivary cortisol 60 min after awakening	22.68 (2.67)	19.20 (1.07)
Cortisol awakening response	9.41 (2.05)	7.86 (1.12)
Chronic stress screening scale	18.88 (2.12)	16.76 (1.54)

Standard errors of the mean are shown in parentheses; Cortisol awakening response is defined as cortisol concentration 30 min after awakening minus cortisol concentration directly after awakening.

right and left turns from a single landmark, such as a tree). Participants could use each of the landmarks (e.g., tree and rock) as a stimulus; however, they were categorized as response learners only if they used a single landmark for navigation. If participants mentioned at least two spatial landmarks and did not mention counting open and closed arms, they were categorized as using a spatial strategy. Neuroimaging data confirmed that response learning and spatial learning as defined above are associated with increased gray matter and functional magnetic resonance imaging (fMRI) activity of the caudate nucleus and the hippocampus, respectively (Iaria et al., 2003; Bohbot et al., 2007). Finally, participants were given Salivettes® and an instruction for saliva sampling after awakening, the questionnaire for the assessment of prenatal stress, as well as the chronic stress questionnaire. Participants were asked to return these materials to the experimenter within 1 week.

RESULTS

Sample Characteristics

About one-third (n = 19) of the tested participants reported that their mother had experienced at least one major negative event during her pregnancy. These participants were assigned to the prenatal stress group. The rest of the participants, whose mothers did not experience any major negative life events during their pregnancy, were assigned to the comparison group. There were no significant differences between the two groups with respect to age, sex, education (of the participant and their mother), or body mass index (all $P > 0.10$; Table 1).

Moreover, the prenatal stress group and the comparison group did not differ in early life stress and acute or chronic stress parameters at the time of testing (Table 1). Groups did not differ in perinatal problems or the number of stressors during childhood (both $P > 0.10$). Concentrations of the stress hormone cortisol as well as the scores on the different dimensions of the mood scale were similar in the two groups before testing started (all $P > 0.10$). Furthermore, there were no group differences in the reported level of chronic stress and the cortisol awakening response (all $P > 0.15$), a physiological indicator of chronic stress (Chida and Steptoe, 2009). Thus, differences between the prenatal stress group and the comparison group in the learning task cannot be attributed to group differences in early life and acute or chronic stress.

Identification of Spatial and Response Learning Strategies

On the basis of their verbal reports, 22 participants were categorized as using a spatial strategy (spatial learners) and 38

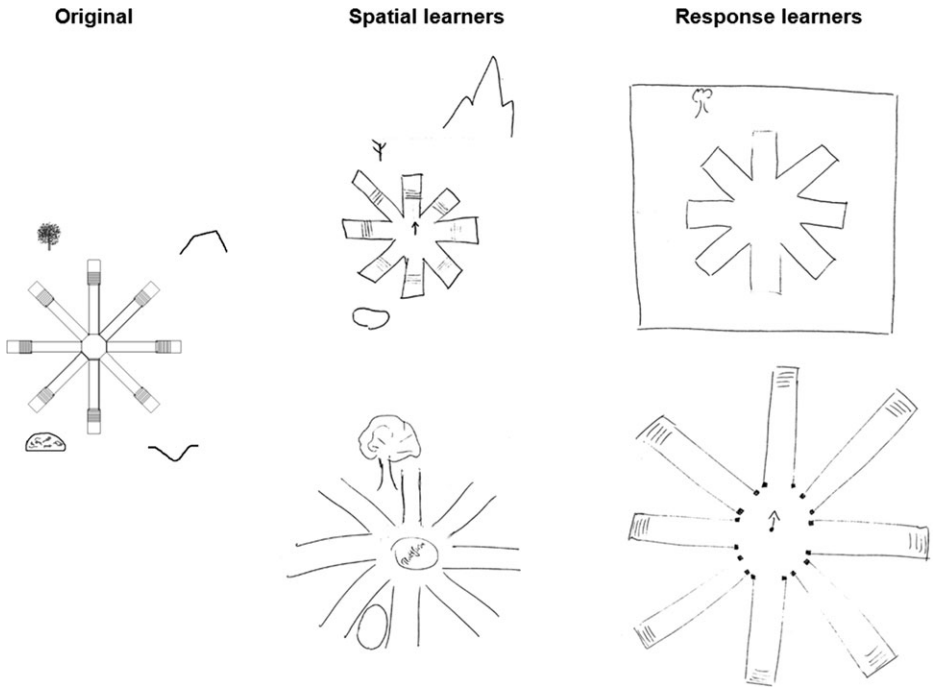

FIGURE 2. Examples of maps drawn by spatial and response learners. Left column: Scheme of the maze including all landmarks; middle column: drawn maps of spatial learners; and right column: drawn maps of response learners. Maps of spatial learners were generally more accurate than those of response learners.

were categorized as using a response strategy (response learners). The overlap between the categorizations of the two independent raters was very high (95.8%), and discrepancies were discussed until an agreement was reached.

The categorization of participants as spatial and response learners was supported by our behavioral data. As expected, participants categorized as spatial learners were significantly impaired relative to response learners in the second part of the probe trial, in which the spatial cues were removed [number of errors: 1.45 (SEM: 0.30) vs. 0.68 (SEM: 0.18), $t(58) = 2.34$, $P = 0.023$, and $d = 0.63$]. Moreover, the drawn maps of the maze and its surrounding were significantly more accurate in spatial learners than in response learners [score: 5.0 (SEM: 0.35) vs. 4.0 (SEM: 0.24; $t(58) = 2.44$, $P = 0.018$, and $d = 0.66$]. Examples of maps drawn by spatial and response learners are shown in Figure 2.

Influence of Prenatal Stress Exposure on Learning

Most participants learned the task quickly. Only 11 of the 60 participants needed an additional training trial. These 11 participants were evenly distributed across the prenatal stress group and the comparison group ($\chi^2(1) = 0.12$ and $P = 0.73$). Learning performance expressed as the number of errors made and the time needed to finish a trial was analyzed by a group (prenatal stress vs. comparison group) $\times$ trial ANOVA. Figure 3 shows that both groups improved significantly across the training trials (main effect trial for the time to finish a trial: $F(3,174) = 7.88$, $P < 0.001$, and $\eta^2 = 0.12$) and that both groups made relatively few errors which tended to increase in the probe trial (main effect trial for errors: $F(3,174) = 1.81$, $P = 0.14$, and $\eta^2 = 0.03$). There were no main effects of group and no group $\times$ trial interactions (for errors and time: all $F < 1$ and all $P > 0.30$), suggesting that prenatal stress exposure did not affect learning performance. Performance in the probe trial was analyzed by a group $\times$ part (part one vs. part two of the probe trial) ANOVA. This analysis also revealed no significant main effects of group and no significant group $\times$ part interactions (all $F < 2.5$ and all $P > 0.12$).

Although prenatal stress did not influence quantitative task performance, it changed the way how participants learned the task (Fig. 4). Prenatal stress exposure biased learning toward more response strategies: the use of a response strategy increased from 54 to 84% and the use of a spatial strategy decreased from 46 to 16% in participants that were exposed to prenatal stress compared with participants whose mothers had not been exposed to major negative events during pregnancy [χ^2 (1) = 5.52 and $P = 0.022$].

In a next step, we tested the effect of negative life events during intrauterine life on the used learning strategies when controlling for the influence of perinatal problems, adverse conditions during childhood, acute and chronic stress, as well as participants' age and sex. We conducted a stepwise multiple regression analysis with the used learning strategy as the dependent variable. We entered our control variables in a first step and the number of negative life events during pregnancy in a second step into the regression model. The overall regres-

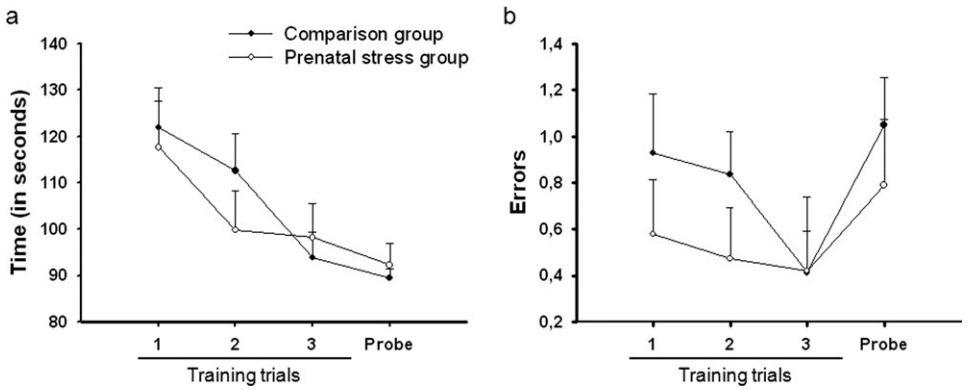

FIGURE 3. Time needed to finish a trial (a) and number of errors made (b) for the prenatal stress group and the comparison group across the three training trials and the probe trial. Data refer to the second part of each trial. Error bars represent SEM.

sion was significant for the second model [$R^2 = 0.29$, $F(7,49) = 2.78$, and $P = 0.027$] but not for the first model [$R^2 = .21$, $F(7,49) = 1.60$, and $P = 0.16$]. The number of negative life events that occurred to participants' mothers during their pregnancy predicted the used learning strategy, even when controlling for perinatal and early life stress, acute stress, chronic stress, age, and sex ($\beta = 0.33$ and $P = 0.042$).

DISCUSSION

Our data demonstrate that prenatal stress exposure affects learning and memory processes in later life. Specifically, we show that young adults whose mothers had experienced major negative life events during their pregnancy used the simple, caudate nucleus-dependent response strategy significantly more often than the cognitively demanding, hippocampus-dependent spatial learning strategy in a navigation task, compared with young adults whose mothers had no such negative experiences during their pregnancy. Individual differences in acute or chronic stress levels at the time of testing cannot explain these findings as the effect of prenatal stress remained when we controlled for acute and chronic stress influences.

How can prenatal stress affect the engagement of different learning strategies in adulthood? Previous studies with the same learning protocol demonstrated that the response strategy is supported by the caudate nucleus, whereas the spatial strategy relies on the hippocampus (Iaria et al., 2003; Bohbot et al., 2007). Thus, the observed effect of prenatal stress may be due to an enhancement of caudate-based learning or to an impairment of hippocampus-based learning (or both). In light of the existing literature, the most likely explanation appears to be that prenatal stress impaired hippocampus-dependent spatial learning. The hippocampus is one of the most stress-sensitive areas of the brain (de Kloet et al., 2005). It expresses stress hormone receptors at a very high density and is affected by stress during critical periods of (brain) development (de Kloet et al., 2005; Lupien et al., 2009). In other words, prenatal stress may "preprogram" the functioning of the hippocampus in later life. This idea is supported by studies in rodents and non-human primates showing that prenatal stress exposure reduced hippocampal neurogenesis and performance in hippocampus-dependent tasks in later life (Lemaire et al., 2000; Coe et al., 2003; Yang et al., 2006).

Prenatal stress biased learning strategies toward more caudate-based response learning but did not affect learning performance per se. This finding is in line with rodent data showing that adult offspring of rats who consumed ethanol during pregnancy favored response over spatial learning strategies but were not impaired in learning (Sutherland et al., 2000). The same pattern of results was found in humans who were exposed to an acute stressor or experienced chronically high levels of stress (Schwabe et al., 2007, 2008). Together, these data suggest that individuals can make use of multiple parallel (hippocampus and caudate-based) learning systems, which are equally able to support performance. These independently functioning parallel systems can appear to compete or to cooperate. They appear to compete when the systems generate different behaviors [e.g., in a fixed location-visible platform water maze task, see (Kim et al., 2001)]. They

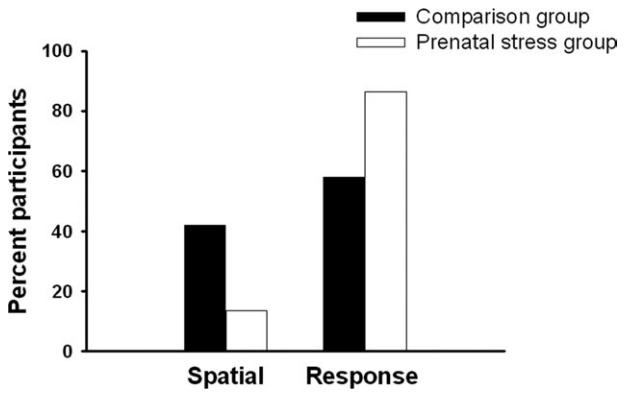

FIGURE 4. Strategies used in the learning task. The reported learning strategies were validated by performance during the probe trial.

appear to cooperate when the two systems generate the same solution to a task (e.g., in the present 4/8 VM). Such "cooperation" may allow one system to compensate for (relative) dysfunctions of the other, for example, in consequence of prenatal stress exposure, to maintain performance (see also, Voermans et al., 2004).

Although prenatal stress did not affect learning performance, the observed shift in the engaged learning strategies reflects a change in the quality of learning. Spatial but not response learning allows the flexible use of the acquired knowledge and the transfer to novel situations (Mishkin and Petri, 1984; Reber et al., 1996). It remains to be seen whether the prenatal stress-related bias toward more rigid response learning would emerge also in other tasks than spatial navigation [for acute stress there is such evidence from an instrumental learning task, see (Schwabe et al., in press)]. If people constantly engage rather rigid learning strategies, at the expense of flexible strategies, this may hinder adaptation to ever-changing environments and can thus have unfavorable consequences in the long run, for example, in social, educational, or work-related settings. Moreover, a predominance of rigid, inflexible learning may also increase the risk for psychiatric disorders such as drug addiction (Robbins and Everitt, 1999; Schwabe et al., 2011). Because response strategies were previously associated with lower fMRI activity (Iaria et al., 2003) and lower gray matter in the hippocampus (Bohbot et al., 2007), consequently, predominance of rigid, inflexible learning associated with response strategies may also increase the risk of neurological and psychiatric disorders associated with lower gray matter in the hippocampus such as schizophrenia (Pantelis et al., 2003), post-traumatic stress disorder (Gilbertson et al., 2002), depression (Amico et al., 2011), and Alzheimer's disease (Apostolova et al., 2006). Animal studies suggest that early postnatal manipulations can ameliorate the negative effects of prenatal stress (Morley-Fletcher et al., 2003; Lemaire et al., 2006). How to counteract the disadvantageous effects of prenatal stress on learning and memory in humans is an important question for future research.

Our behavioral data parallel those previously reported in rats (Sutherland et al., 2000). As previously shown in rats, prenatal stress had no effect on learning curves but instead led to an increased probability of rigid response strategies. Despite these parallels, important methodological differences between rodents and humans should be considered. First, although our participants completed only three to five trials, presented one after another on the same day, rats were trained in more than 40 trials over a period of 12 days. Another major methodological difference that can explain the different learning curves between rodents and humans is that humans are given verbal instructions, whereas rodents must learn the task by trial and error. Moreover, the water maze task that was used is aversive and the escape platform acted as a negative reinforcer. Our task, however, is appetitive because most individuals consider navigating in a virtual environment to be pleasant. Therefore, our participants may have differed in their emotional and motivational states relative to rodents. These differences may be important and may affect learning processes. Nevertheless, pharmacological and lesion data in rodents (McDonald and White, 1993; Packard and Teather, 1998) and human neuroimaging data (Iaria et al., 2003) suggest that the same brain areas are involved in spatial vs. response learning strategies in rats and humans.

The fact that stress, whether acute or chronic, affects learning strategies is well documented [for a review, see (Schwabe et al., 2010b)]. The present data suggest that stressful experiences during intrauterine life may influence how we learn a task as adults. Prenatal stress exposure increased the engagement of caudate nucleus-based response learning strategies at the expense of hippocampus-based spatial learning strategies. This shift in the used learning strategies may have negative consequences for the flexibility with which the acquired knowledge can be used (Mishkin and Petri, 1984; Reber et al., 1996). Although there is hope that the adverse effects of prenatal stress can be counteracted later on (Morley-Fletcher et al., 2003; Lemaire et al., 2006), our findings show that some of the inter-individual differences in learning and memory may have their roots very early in life.

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