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RESEARCH ARTICLE

Effect of early maternal separation stress on attention, spatial learning and social interaction behaviour

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Abstract

Early life stress is known to influence affective and cognitive functions in later life but comprehensive explanation for the impact of early life stress on attentional functions, behavioural control and social behaviour is inadequate. The early life stress was induced by exposing rat pups to 6 h of maternal separation and isolation (MS) stress from postnatal days 4–14 i.e. during SHRP period. The long-term impact of MS in these rats was evaluated by assessing anxiety, sociability, social preference, spatial learning and memory along with a detailed evaluation of attentional functions during young adulthood period. Adult male MS rats showed increased anxiety-like behaviour, impaired flexibility in social interactions, and increased reward-seeking behaviour. MS rats also showed faster spatial learning in the partially baited radial arm maze and exhibited moderately enhanced sustained attention in the 5-choice serial reaction time task (5CSRTT). These results suggest that early MS has both positive and negative consequences in adulthood. Increased cognitive ability in MS rats, as evidenced by the improved sustained attention and spatial learning and memory, is usually advantageous and indicates positive influences of early stressors that might lead to the development of resilience and enhanced compensatory mechanisms later in adulthood. MS stress has compromised flexibility in social behaviour that promotes solitary lifestyle and social isolation. Heightened reward-seeking behaviour, as shown by the MS rats, could be a predisposing factor for substance abuse and addiction. Thus, our study highlights the crucial and differential impact of early life challenges on behaviour during adulthood and suggests that the positive aspects could be an asset that may be utilized to suppress the negative effects of early life stress in adulthood.

Keywords Maternal separation stress (MS) · 5-Choice serial reaction time task (5CSRTT) · Sustained attention · Perseveration · Cognitive flexibility · Learning and memory · Anxiety

Introduction

Maternal care plays an important role in brain development and maturation (Champagne et al. 2003; Liu et al. 1997). Bowlby was the earliest to show that disruption in early maternal care would hamper the development of brain and behaviour and proposed the attachment theory (Andersen 2005; Bowlby 1954). Studies have shown that an early life stress rodent model that disrupts maternal care, called 'maternal separation and isolation stress' (MS), has profound impact on postnatal brain development affecting functional maturation of critical brain regions involved in cognitive and affective functions (Becker et al. 2007; Carlson and Sroufe 1995; McEwen 2000; Oitzl et al. 2000).

The early postnatal period, specifically postnatal day (PND)4–PND14 in rats, is crucial for the ontogeny of the stress system and is termed as the stress hyporesponsive period (SHRP) (Levine 1994; Schapiro et al. 1962; Schmidt et al. 2003; Walker et al. 1986). In this period, there is minimized stress responsiveness leading to a window for synaptic pruning and formation of a functional network of critical brain regions that mediate and regulate stress response later in life. During these early postnatal days, specific maternal behaviours involving licking and grooming modulate the HPA axis by inhibiting or reducing its activity (Levine

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1956, 1957, 1960; Levine and England 1960). Stress, particularly MS, during SHRP, leads to increased corticoid levels in the circulation during adulthood (Liu et al. 2000). These alterations are mostly the consequences of synaptic changes within functional neuronal networks (Bock et al. 2005) affecting maturation of critical brain regions (Benes et al. 2000). Several lines of evidence suggest that such early life stressors lead to abnormally high synaptic density in medial prefrontal cortex (mPFC) (Ovtscharoff and Braun 2001), reduced dendritic spines in anterior cingulate cortex (ACC) (Bock et al. 2005) and increased amygdalar volume (Lupien et al. 2011) causing functional impairment. Our earlier study had also shown that MS during SHRP sensitizes the hippocampus–amygdala–cortical neural network later in life during young adulthood (Sampath et al. 2014).

Complex behaviours involving cognitive control or emotional regulation require the coordinated activity of multiple brain regions. MS stress-induced alterations in neural networks could, therefore, manifest as mood disorders and cognitive impairments in adulthood (Newport et al. 2002). Several studies in MS rats have shown impairments in affective functions including increased anxiety-like behaviour (Aisa et al. 2007; Huot et al. 2001; Salm et al. 2004; Wigger and Neumann 1999), depressive-like behaviour (Aisa et al. 2007; Hall et al. 1998; Ladd et al. 2000; Plotsky et al. 1998; Willner 1990) and anhedonic behaviour (Huot et al. 2001; Willner et al. 1987; Zurita et al. 1999). Cognitive impairments such as learning deficits in Morris water maze and object recognition test (Aisa et al. 2007; Garcia et al. 2013) have also been reported. Further, we have previously reported that MS stress in rats results in increased anxiety behaviour in adulthood (Dayalan Sampath et al. 2010), along with enhanced fear memory and fear generalization (Sampath et al. 2014).

On the other hand, there have been studies implicating the cognitive enhancements (Makena et al. 2012; Oomen et al. 2010) and improvement in affective functions too upon early life stress exposure (Chocyk et al. 2014; McCoy et al. 2016; Rana et al. 2015). These variable findings about the effect of early life stress on adulthood cognitive and affective functions suggest that there is a need for studies that systematically evaluate both cognitive and affective functions to better understand the impact of MS on brain and behaviour. Importantly, these variabilities in findings could be due to different factors such as duration, type, and timing of neonatal manipulation and sex and strain of animals (Kosten et al. 2012). To address these issues, one possible solution would be to study these various cognitive and affective behaviours in single MS model.

Particularly, social behaviour and attention-related aspects are not well explored in early life stress models. Attention is a crucial component for learning and memory in both affective and cognitive domains (De Brigard 2012). A few studies had assessed attentional aspects in early life stress but (Colorado et al. 2006; Lovic et al. 2011) these reports also provided inconsistent findings: one study showed no effect of MS on attention (Kentrop et al. 2016) while others showed improved attentional abilities (Boutros et al. 2017; Lehmann and Feldon 2000; Lehmann et al. 1998) and a few others reported impaired attentional processing following MS in rats (Carlyle et al. 2012; Ellenbroek et al. 1998; Fuentes et al. 2014; Tzanoulinou et al. 2016; Wilson et al. 2012).

Although there are few studies where two or few behaviours are being assessed with single MS model, comprehensive studies are not found in the literature yet. Therefore, the present study has carried out a series of experiments that spanned both cognitive and affective domains with an emphasis on attentional functions. This would be more appropriate and would better represent the human conditions as human subjects may not only present one or two symptoms, instead a cohort of symptoms spanning both cognitive and emotional domains. Since social behaviour involves both components of cognitive and emotional aspects, the study also assessed different forms of social behaviour in MS rats.

Materials and methods

Subjects

Male Wistar rats of 2–3 months were used for the present study. These rats were housed 3–4 per cage in Central Animal Research Facility (CARF), NIMHANS, Bengaluru in a climate-controlled room having light–dark cycle with food and water available ad libitum. All the experiments were conducted according to the ethical guidelines of the NIMHANS Institute and approved by the Institutional Animal Ethics Committee (AEC/54/338/N.P./M.K) of NIMHANS, Bengaluru.

Female rats with 18–19 days of pregnancy were procured from CARF, NIMHANS and maintained in 12:12 h light:dark cycle (from 8.00 a.m. to 8.00 p.m. light was 'on' and from 8.00 p.m. to 8.00 a.m. lights were 'off'). The day of delivery was considered as postnatal day zero (PND0). Maternal separation and isolation (MS) stress procedure was carried out from PND 4–PND 14. The total number of dams used in the present study was 18 (9 litters for MS stress and 9 litters for Control). During MS procedure, male and female segregation was not performed. Male and female segregation was performed later during the weaning period. All the experiments carried out in male rats and female rats returned to the CARF for rehabilitation procedures.

Maternal separation and isolation stress (MS) procedure

The rat litters were housed with dam in a cage for the entire period of pre-weaning period except at the time of maternal separation procedure. MS procedure was followed as mentioned previously (Mishra et al. 2019). MS procedure began on postnatal day 4 by the removal of dam from their littermates first and kept in a fresh home cage. The litters were then assigned to maternal separation protocols wherein the rat pups were kept individually isolated from each other in home-cage-like environment having 6 partition cubicles. The temperature was maintained at 25 °C. The maternal separation and isolation stress were done for a period of 6 h (10.00–16.00 h) daily from PND4 to PND14. No nutritional supplements were provided during separation procedure because milk pouch was full before the start of separation procedure. Previous studies have shown that isolated housing of pups during maternal separation protocol has more impact on adulthood behaviour rather than group housing of pups. Therefore, the isolation along with separation was adopted in this protocol. At the end of the separation period, both pups and dam were returned to the home cage.

Normal controls without MS stress (NMS) rats

The group of rats and dams remained untouched except for regular bedding changes until the weaning day P21. On P21, the rat pups were weaned from the mother and housed 3–4 rats per cage until they were subjected for behavioural experiments.

Experimental procedure

Rats were of 2–3 months old when used for experiments. All experiments were done with male Wistar rats. The schematics is described in detail about the experimental design as in Fig. 1. Different cohort of rats was used for each task as mentioned in the experimental design. Rats from multiple litters formed a cohort and such different cohorts were used for each experiment. All the experiments performed between 12.00 and 20.00 h and the ambient temperature of the laboratory was 28 ± 2 °C.

Anxiety test

Augmented and uncontrolled anxiety is commonly seen among psychiatric patients. However, etiological factors of anxiety are not clearly known. In the present study, baseline reactivity to elevate anxiety response was tested in a light–dark apparatus (Crawley 1985).

Apparatus

The apparatus (Coulbourn Instruments, USA) consisted of light and dark compartments, each 26 × 26 cm and connected by 8 × 8 cm guillotine doorway. The light chamber was illuminated with a bright light (> 120 lx) on the ceiling. The door was programmed to open at the 5th second immediately after initiating the protocol.

Procedure

The procedure was followed as mentioned previously (Dayalan Sampath et al. 2010). Rats from both NMS and MS group were individually placed in brightly lit environment and allowed to explore freely in both light and dark environments. The anxiety test was for 10 min for each rat. Five second after the placement in the brightly lit environment, door to dark chamber opens. The time taken to enter into the dark chamber was noted down as latency to enter into dark compartment. In addition, the time spent in the

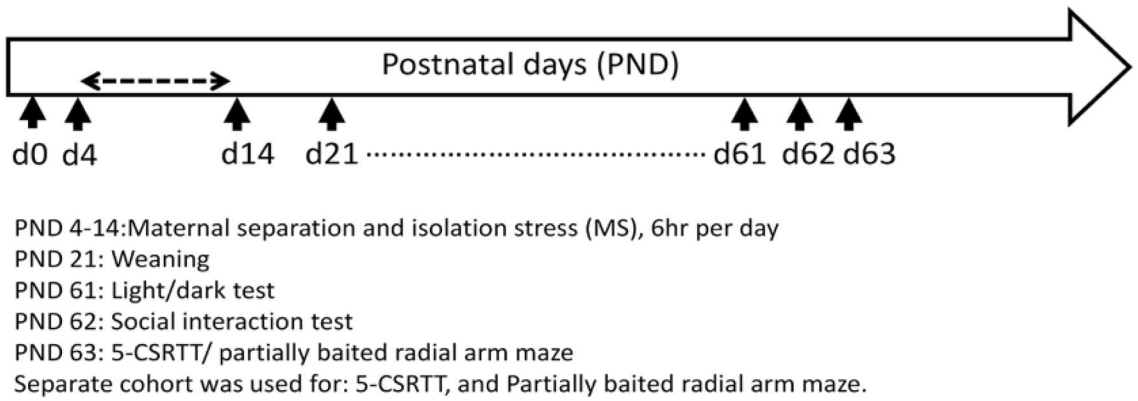

Fig. 1 Outline of the study: Describes the details of schedule for behavioural experimentation and MS procedure performed. Rats from multiple litters formed a cohort and each experiment was performed with different cohorts

dark environment and the number of transitions between the compartments were quantified offline. The parameters, time spent in dark chamber and latency to enter the dark chamber served purely as measures of anxiety behaviour and number of transitions served as indicator of both anxiety behaviour and locomotor activity.

Social interaction test

Rat's ability to interact with novel object and novel subject was tested in a three-chamber social interaction task (Moy et al. 2004). It was developed to assess the social cognition in a much simpler way of social interactions in terms of sociability and social novelty behaviour.

Apparatus

The test apparatus consisted of clear Plexiglas (Axxonet Systems Technologies, Bengaluru) divided into three chambers proportionately size adjusted (120 cm × 90 cm × 40 cm) to provide comparable social proximity for adult rats with each chamber of a size (40 cm × 90 cm × 40 cm), the two peripheral chambers are separated from the middle section with a Plexiglas plate which had a slot of 20 cm wide for rat movement between the chambers. Initially, the middle chamber was isolated from the other two adjacent chambers by placing two removable white Plexiglas plate separators during habituation.

Procedure

Our protocol was adapted from previous studies (Anshu et al. 2017). All testing procedures were conducted with light of ~ 150 lx. Prior to testing, an experimental rat was allowed to habituate by placing in a middle section for 5 min. After this habituation period, a stranger rat1 in metal holder (S1) to restrict movement of stranger rat was placed in one adjacent chamber and on the other adjacent chamber an empty metal holder (O) was placed. Now, the experimental rat was allowed to explore the two adjacent chambers by removing the white Plexiglas plate separators. Duration of 10 min was given for an experimental rat to explore all the chambers. The time spent in the chamber, with stranger rat1 (S1) and with the empty metal holder (O), was calculated separately, these are the indices of sociability or social motivation. If an experimental rat is sociable, then it will spend more than 50% of given time in the stranger rat (S) chamber than in empty metal holder chamber (O). In social novelty test, the empty metal holder was replaced with another stranger rat2 (S2) in a metal holder. Again 10 min duration was given for the experimental rat to explore between now familiar rat (S1) and a novel rat (S2). There was an inter-trial interval of 5 min between first social interaction test and second social novelty tests. The stranger rats were of same strain, same sex and 15–20 days younger than the test rats. Stranger rats were never exposed to test rats before the social interaction test. The entire apparatus was cleaned with 70% alcohol between the tests for all experimental rats.

Partially baited radial arm maze (PBRAM)

The eight-arm radial maze (RAM) consisted of eight equally spaced arms (42 × 11.4 × 11.4 cm) radiating from an octagonal central platform (Columbus Instruments, Ohio) and the maze was kept 120 cm elevated from the ground. Before the training, the animals were kept on a restricted diet, and body weight was maintained at 85% of their free feeding weight with water available ad libitum. The procedure was followed as mentioned previously (Srikumar et al. 2007).

At the beginning of RAM experiments, rats were given 2 days of habituation and shaping sessions, in which they were individually allowed to explore the maze for 10 min each day and eat all the food pellets (Kellogg's Planets and Stars™, Kellogg India, Mumbai, India) placed in all the arms of the maze. During RAM training, bait was placed semi-randomly only in four selected arms and was same for all rats ensuring that the spatial relations between baits positions and the distal visuo-spatial cues were same for all animals. Training was given until all the rats cross learning criteria of 80% correct choice that may take up to about 14–16 days. Experiments were run every day between 8 a.m. and 3 p.m. During daily sessions, rats were individually placed on the central platform facing different directions and allowed to orient themselves. Rats were permitted to choose among the arms until they completed the session by either entering all the baited arms or 5 min had elapsed, whichever is first. The maze was cleaned of cues and droppings after each rat with 70% alcohol.

A partially baited radial arm maze allows simultaneous estimation of percent correct choice, reference and working memory errors. Behavioural measures included (a) total number of correct choice into baited arms (percent correct choice), (b) total number of entries to unbaited arms (reference memory errors, RME), and (c) total number of re-entries to either baited or unbaited arms (working memory errors, WME). Thirty days after acquisition of the task, rats were once again evaluated for retention of remote spatial memory. Rats were given two trials, and the average of two trials was taken for analysis.

Sustained attention using 5-choice serial reaction time task

This task was performed to assess sustained and spatially divided attention in rats (Bari et al. 2008; Robbins 2002). Our protocol was adapted from previous studies (Anshu

et al. 2017; Bari et al. 2008). Before the initiation of study, rats were food deprived for 3 days and maintained at 85% of their free-feeding weight but water was provided ad libitum. Testing for the attention task was carried out during 12.00–20.00 h.

Apparatus for 5-choice serial reaction time task

The behavioural training and testing were performed in an isolated chamber consisting of 25 cm × 25 cm aluminium chamber (Coulbourn Instrument, USA). The side wall of the chamber is concavely curved and had five deep holes, each 2.5 cm^2, 4 cm deep and set 2 cm above floor level. Illumination of each hole was provided by three standard 3-W bulbs located at the rear end of the hole. In addition, located at the entrance of each aperture is an infra-red photocell beam for monitoring the nose poke responses by the rat. The opposite wall is equipped with a magazine connected to the automated pellet dispenser. Also there is a house light on top of the same wall (3 W) which can be modulated for illumination according to the task protocol. The floor of the chamber was a spaced grating of parallel steel bars (Coulbourn Instruments, USA). The chamber is housed within sound-attenuating cabinet and is ventilated by low-level noise fan, which also served to mask extraneous background noise. This chamber is connected to a computer from which all the protocols are developed and executed with the software Graphic State version 3.3.

Experimental procedure

Acquisition

On the first day, rats were allowed to explore freely for 10 min in the testing chamber with the house light 'ON'. During this session, rats were allowed to explore to get familiarized with the food magazines, nose poke holes and testing chamber for 2 days.

After 2 days of familiarization, on day 3, rats were habituated to the operant chamber by placing the pellets in all the holes and the food magazine. The house light and the light in all the holes and food magazine were 'ON' during this session. Each session lasted for 15 min per day for 3 days.

On day 6, the first phase of shaping procedure began for the rats to poke the nose to receive the reward; rats were trained continuously for 2–3 days to poke the nose in any one of the holes to receive the pellet which was delivered automatically into food magazine after a poke in any hole. Here in all the holes, light was 'ON' and whenever a poke is made in any hole, the light gets 'ON' in food magazine, simultaneously delivering a pellet. This session lasted for 15 min for each rat per day.

In the second phase of shaping procedure on day 9, rats were presented with the light 'ON' in one of the five holes for the nose poke to receive the food delivery; totally, 100 trials were presented per session per day with 30 min duration. This procedure is carried out for 3–4 days. Once the rats reach criterion of 50 correct nose pokes in 30 min, rats are said to have successfully acquired the protocol. Behavioural testing did not commence until after all rats achieved the final shaping criterion. The shaping of any individual rat did not exceed 7 days.

Training for the sustained attention

The training session begins with the illumination of the house light and food magazine. At first, house light was ON and a nose poke in the magazine initiates the first trial followed by delivery of a food pellet. After a fixed inter-trial interval (ITI) of 5 s, one of the five holes is randomly illuminated for a brief period of 30 s (stimulus duration) and a nose poke (correct response) in that hole, while the LED is 'on' or in an additional short duration called limited hold period of 5 s, leads to illumination of magazine light reinforcing the delivery of food pellet. A nose poke into magazine to collect the pellet initiates the next trial with ITI. If a nose poke in any hole other than the one with light 'on' corresponds to incorrect response. Failure to respond at all is called omission and the responses during the ITI, i.e. before the light is lit in any holes, are indicated as premature responses. These three highlighted behaviours are not reinforced but are signalled by a time out period of 5 s darkness in the chamber. At the end of time out period, house light turns 'on' and next trial begins with ITI.

Each session includes 100 trials or 30-min duration with one session per day. Each session concludes after 30 min or when rats complete 100 trials within 30 min. During any one session, the light stimulus was presented an equal number of times in each of the five apertures or holes in a random order. The rats were considered to have reached criterion when the target parameters were attained on at least three consecutive sessions with ≥ 80% correct responses and < 20% omissions within the 30 min session time. For every stage of stimulus duration, a rat would reach the criterion with ≥ 80% correct response to go for the next stage of reduced stimulus duration. There are 6 stages of stimulus duration, first is 30 s followed by 10 s, 5 s, 3 s, 2 s and finally 1 s for testing. Approximately, 20–30 sessions were required for the rats to complete all the stages.

At the completion of the baseline sessions at 2 s stimulus duration, testing in a challenge session at 1 s stimulus duration to assess performance in high attentional load was carried out. After attentional challenge test, to assess the effects of stimulus unpredictability and control of responding during the ITI period, rats were exposed to a session of random

variable ITI's (5 s, 10 s, 15 s). The session length for the vITI challenge was same as for baseline sessions, i.e. 30 min. Equal numbers of each vITI were randomly presented during the 100-trial session.

Performance measures

Accuracy of performance was measured as the proportion of responses that were correct (number of correct responses/total number of correct and incorrect responses), expressed as a percentage. Errors of omission were also presented as percent omissions; this measure reflects possible failures of detection and also motivational/motor deficits, depending on the overall pattern of effects.

Two measures of behavioural inhibitory control were assessed. Premature responses were the number of responses made in the holes during the ITI. Such responses occur inappropriately, before the onset of the light in any hole and presumably during the period in which the rat anticipates their occurrence. Thus, this measure reflects inhibitory mechanisms of response preparation and is closely related to impulse control (Bari et al. 2008). By contrast, perseverative responses were repeated responses in the holes following a correct response. Thus, this measure reflects inhibitory processes of response control more likely to be 'compulsive' behaviour rather than 'impulsive' behaviour.

Speed, including decision time, was assessed according to three different latencies. The first was the latency to respond correctly, defined as the time between the onset of the visual stimulus and the point at which the animal's nose breaks the infra-red beam of the lit hole. The second measure was the latency to respond incorrectly, defined as the time between the onset of the visual stimulus and the nose poke into an unlit hole. Third measure was reward latency: the time between performance of a correct response and collecting the pellet from magazine panel may suggest a motivation factor.

Data analysis

Data are presented as mean ± SEM. NMS and MS served as between-subject factors. All the data are screened for normality with D'Agostino and Pearson omnibus normality test followed by outlier removal by ROUT Method in Prism 7. Raw data for 5CSRTT were imported into MATLAB v2013a (MathWorks Inc., USA) for analysis of nose poke latency, reward latency and perseverative responses. A paired and unpaired Student's *t* test was used for parametric data and Mann–Whitney test was used for non-parametric data to assess the effect of MS on performance. Wherever necessary normal two-way ANOVA or repeated measures of two-way ANOVA was performed. To compare both groups on entire acquisition performance, repeated-measures ANOVAs were performed. For every statistical test that is reported, the first result of Student's *t* test '*t*' and '*p*' value was used, for Mann–Whitney test results '*p*' value was used and for ANOVA tests '*F*' value is presented with the degrees of freedom. Any further results of the post hoc statistical test were reported with *p* value only. The criterion for statistical significance was a probability level of $p < 0.05$ and trend at $p \leq 0.1$. The symbol for significant within-group differences was '#' and for trend 'Δ' was used and symbol for between-group significant difference '*' was used and for trend '^' was used. Statistical software (Prism 7) was used for analysis.

Results

Effect of early maternal separation and isolation stress on anxiety-like behaviour when subjected to anxiety provoking environment

In the present study, we observed potentiated anxiety in rats during adulthood. When subjected to brightly lit environment in light–dark chamber, MS rats displayed heightened anxiety-like phenotype and showed significant increase in the time spent in a dark chamber ($t_{22} = 2.302$, $p = 0.031$) (Fig. 2a), a trend for reduction in number of transitions between chambers ($t_{24} = 2.061$, $p = 0.050$) (Fig. 2b) and a significantly reduced latency to enter the dark chamber ($t_{24} = 2.614$, $p = 0.015$) (Fig. 2c). In addition, we assessed the body weight of rat pups during three time points, before subjecting the pups to MS procedure (on PND4), after the completion of MS procedure (on PND15) and on PND21 during weaning. We found a significant decrease in body weight of rat pups subjected to MS procedure as compared to NMS rat pups ($t_{30} = 2.326$, $p = 0.027$) on PND15. However, we did not see any group differences in weight on

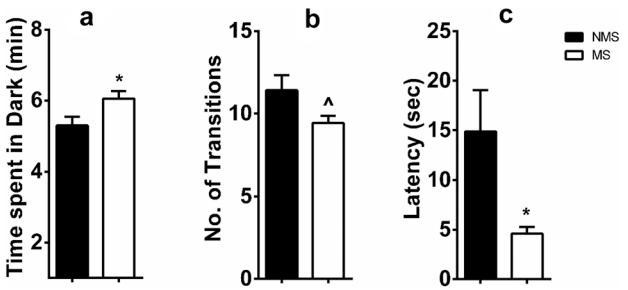

Fig. 2 Effect of MS on anxiety-like behaviour in light–dark paradigm: **a** Time spent in dark compartment, **b** number of transitions between light and dark compartment and **c** latency to enter into the dark compartment. NMS = 14; MS12. Data were analysed by unpaired *t* test and data are represented as mean ± SEM. $*p < 0.05$, $^{\wedge}p < 0.1$ in comparison with NMS group. *NMS* non-maternal separation stress (control) group, *MS* maternal separation stress group

PND4 and PND21 (Supp.4). This shows that MS protocol was associated with reduced weights of the MS pups. However, this effect was temporary as MS pups regained their normal weights within a few days after the completion of the MS protocol.

MS modulates social behaviour particularly the social novelty behaviour but not sociability

Social behaviour, as evaluated with the 3-chamber social interaction test, revealed that MS rats were not different from NMS rats in terms of sociability. There was no main effect of MS stress on sociability ($F_{(1, 23)} = 0.152$, $p = 0.700$) but there was a main effect of Chamber ($F_{(1, 23)} = 57.26$, $p < 0.001$); both NMS and MS rats spend significantly increased time in the chamber S1 than with the chamber containing object (NMS and MS: $p < 0.001$; Sidak multiple comparison test). There was no significant interaction effect of MS effect × Chamber ($F_{(1, 23)} = 0.062$, $p = 0.805$). Thus, sociability was not influenced by MS stress (Fig. 3a) indicating that sociability behaviour is not affected following early life stress.

Further in social novelty test (Fig. 3b), there was no main effect of MS stress on social novelty ($F_{(1, 48)} = 0.003$, $p = 0.955$) but there was significant main effect of Chamber ($F_{(1, 48)} = 11.02$, $p = 0.002$). Also there was significant interaction of MS stress × Chamber ($F_{(1, 48)} = 44.00$, $p < 0.001$). Sidak's multiple comparison test revealed that MS rats spent significantly increased time with the now familiar rat (S1) rather with the novel rat (S2) ($p < 0.001$) but NMS rats showed a trend of increased time spent with the novel rat (S2) ($p = 0.056$). These results suggest that MS rats have impaired social novelty behaviour that may be indicative of social inflexibility in behaviour. Overall, these results indicate that sociability or social motivation was not influenced by MS but social novelty was impaired during adulthood in MS rats.

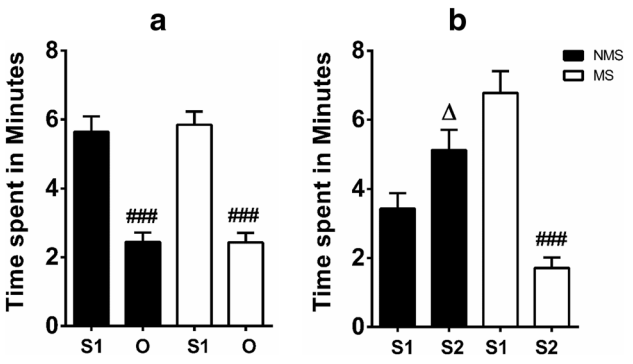

Fig. 3 Effect of MS on social behaviour: **a** sociability test, **b** novelty test. NMS = 14; MS12. Data were analysed by two-way ANOVA test followed by Sidak's multiple comparison test and data are represented as mean ± SEM data. $^{###}p < 0.001$ within-group comparison to S1, $^{\Delta}p < 0.1$. *S1* stranger rat1, *S2* stranger rat 2, *O* inanimate object. *NMS* non-maternal separation stress (control) group, *MS* maternal separation stress group

Maternal separation stress impact on spatial learning and memory in partially baited radial arm maze task (PBRAM)

This task was performed to assess spatial learning and remote spatial memory. Percent correct choice served as a spatial learning index (Fig. 4) indicating that the learning curve was observed in both groups. All subjects showed increase in correct choices as a function of progressive learning as evidenced by significant main effect of training ($F_{(16, 160)} = 46.18$, $p < 0.001$). Early MS stress had main effect on spatial learning in PBRAM ($F_{(1, 10)} = 9.988$, $p = 0.010$), and there was an interaction of PBRAM training × MS stress ($F_{(16, 160)} = 2.780$, $p < 0.001$). NMS rats reached 80% correct choice on 13th day but MS rats reached this criterion as early as on 8th day. MS rats showed significantly increased learning abilities by performing better than NMS rats early during the learning phase. Sidak's multiple comparison test revealed that on day 9 and 11, MS rats showed significantly better performance than NMS rats (Day 9 $p = 0.007$; Day 11 $p = 0.019$). The retention after 30 days, i.e. remote spatial memory was similar in MS and NMS rats ($p = 0.964$). These results suggest that there may be a strong influence of MS on spatial learning but not on spatial remote memory retrieval. Our results indicate that MS stress

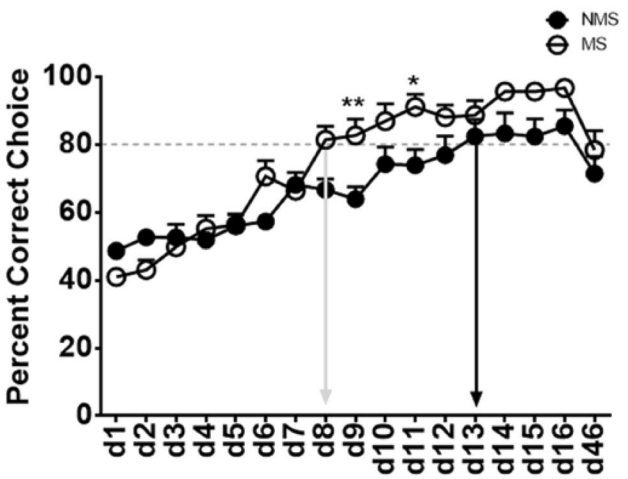

Fig. 4 Maternal separation stress effect on spatial learning and memory in 4-arm partially baited radial arm maze task: percent correct choice as a spatial learning index. Please note that MS rats reached 80% correct choice on day 8, but NMS rats reached the same on day 13. NMS = 11; MS = 11. Data were analysed by two-way ANOVA repeated measures followed by Sidak's multiple comparison test, and data represented as the mean ± SEM, $^{*}p < 0.05$, $^{**}p < 0.01$ in comparison to NMS. *NMS* non-maternal separation stress (control) group, *MS* maternal separation stress group

enhanced spatial learning capacities of rats as evidenced in radial arm maze task.

Impact of MS on training in the 5-choice serial reaction time task (5-CSRTT)

5-CSRTT had different stages of training, with gradual reduction in stimulus duration, to assess attention ability and behavioural control in these rats.

Since MS during SHRP increased anxiety level in rats, it was speculated that increased anxiety could alter the attention ability of these animals. MS did not alter the percent accuracy ($F_{(1, 26)} = 2.228$, $p = 0.148$), omissions ($F_{(1, 26)} = 0.001$, $p = 0.978$) and premature responses ($F_{(1, 26)} = 0.769$, $p = 0.388$) during 5-CSRTT training as compared to NMS rats (Fig. 5) as analysed with two-way RM ANOVA. As the training progressed, both groups of rats showed increased accuracy over the sessions ($F_{(14, 364)} = 56.78$, $p < 0.001$) (Fig. 5a). The number of omissions also increased when stimulus duration was shortened ($F_{(14, 364)} = 14.28$, $p < 0.001$) (Fig. 5b) but premature responses decreased over the sessions ($F_{(14, 364)} = 12.74$, $p < 0.001$) (Fig. 5c). There was no interaction between MS × Training in terms of accuracy ($F_{(14, 364)} = 1.677$, $p = 0.058$) or omissions ($F_{(14, 364)} = 0.921$, $p = 0.536$), but there was an interaction between MS × Training for premature responses ($F_{(14, 364)} = 2.151$, $p = 0.009$). Bonferroni's post hoc test revealed that when compared with NMS group, MS rats showed significant reduction in accuracy during first ($p = 0.0194$) and third day of 30 s SD session ($p = 0.0185$). Similarly, MS rats showed increased premature responses during second day of 30 s SD session ($p = 0.008$) when compared to NMS rats but MS rats did not show significant differences in omissions. Percent accuracy remained above the criterion level of 80% (Fig. 5a) and omissions were less than 20 (Fig. 5b). Therefore, in spite of initial differences, both groups of rats showed similar performance with increasing attentional load during 5-CSRTT training.

Performance at the End of Training (Baseline)

At the end of training (2 s stimulus duration), both groups showed stable baseline accuracy over three consecutive days (Fig. 5d), omissions and premature responses (data not shown). Rats from both groups completed almost 100 trials within 30 min and reached the learning criteria, i.e. accuracy $^{>}$ 80% and omissions $^{<}$ 20. Accuracy, premature responses and omissions were not affected by MS (Accuracy: $F_{(5, 77)} = 1.200$, $p = 0.317$; omissions: $F_{(5, 77)} = 0.618$, $p = 0.686$; premature responses: $F_{(5, 77)} = 0.270$, $p = 0.928$) and stayed well within the acquisition criterion over three consecutive sessions and overall performance was stable (Fig. 5d–f). MS rats performed similar to NMS rats in terms of total trials completed ($t_{26} = 0.962$, $p = 0.345$) and total errors ($t_{26} = 0.308$, $p = 0.760$) (Fig. 5g, h). We assessed speed of processing via correct and incorrect response latencies and motivation using reward collection latency. There were no significant differences in latencies of correct response ($t_{26} = 0.242$, $p = 0.810$) and incorrect responses ($t_{26} = 0.368$, $p = 0.716$), but there was a trend of decrease in reward collection latencies in MS rats ($t_{26} = 1.92$, $p = 0.066$) (Supp.1c–e). Further, MS rats showed a trend towards decrease in repetitive responses in stimulus hole compared to NMS rats ($t_{26} = 2.007$, $p = 0.054$) (Supp.1f) and repetitive magazine entries after reward retrieval were similar in both the groups ($p = 0.166$) (Supp.1g).

In summary, the baseline performance was stable and similar in both groups, as indicated by indices of attention and behavioural control. MS had no influence on speed of processing or motivational factors.

Correlation analysis of MS-induced anxiety on baseline performance

We performed correlation analysis to understand the impact of MS-induced anxiety on sustained attention. The correlation was moderately positive for NMS rats (Supp.1a), indicating an association of basal anxiety with attentional capacities (Pearson $r = +0.201$) but there was strong positive correlation between MS-induced anxiety and attentional performance during baseline recording (Supp.1b) (Pearson $r = +0.608$). This analysis may reveal that enhanced anxiety might augment the attentional capabilities in MS rats.

Attention challenge with short stimulus duration (1 s)

Attention was further challenged with shortened stimulus duration (1 s) as compared to baseline condition (2 s). Both the NMS and MS rats finished almost all trials within 30 min. Two-way ANOVA revealed that the Challenge (increased attentional load) had significant main effect on percent accuracy ($F_{(1, 26)} = 20.89$, $p < 0.001$), leading to decreased percent accuracy in NMS rats ($p = 0.003$) and in MS rats ($p = 0.013$) but magnitude was less for MS rats (Fig. 6a). There was no interaction of MS stress × Challenge ($F_{(1, 26)} = 0.313$, $p = 0.580$). There was a main effect of Challenge on percent omissions ($F_{(1, 48)} = 7.307$, $p = 0.009$). Increased attention load challenge had significantly increased percent omissions (Fig. 6b) in NMS rats (within group; $p = 0.002$) but not in MS rats (within group; $p = 0.985$). There was an increased percent omissions in NMS rats compared to MS rats that led to a statistical significant reduction of percent omissions (Fig. 6c) in MS rats ($p = 0.648$).

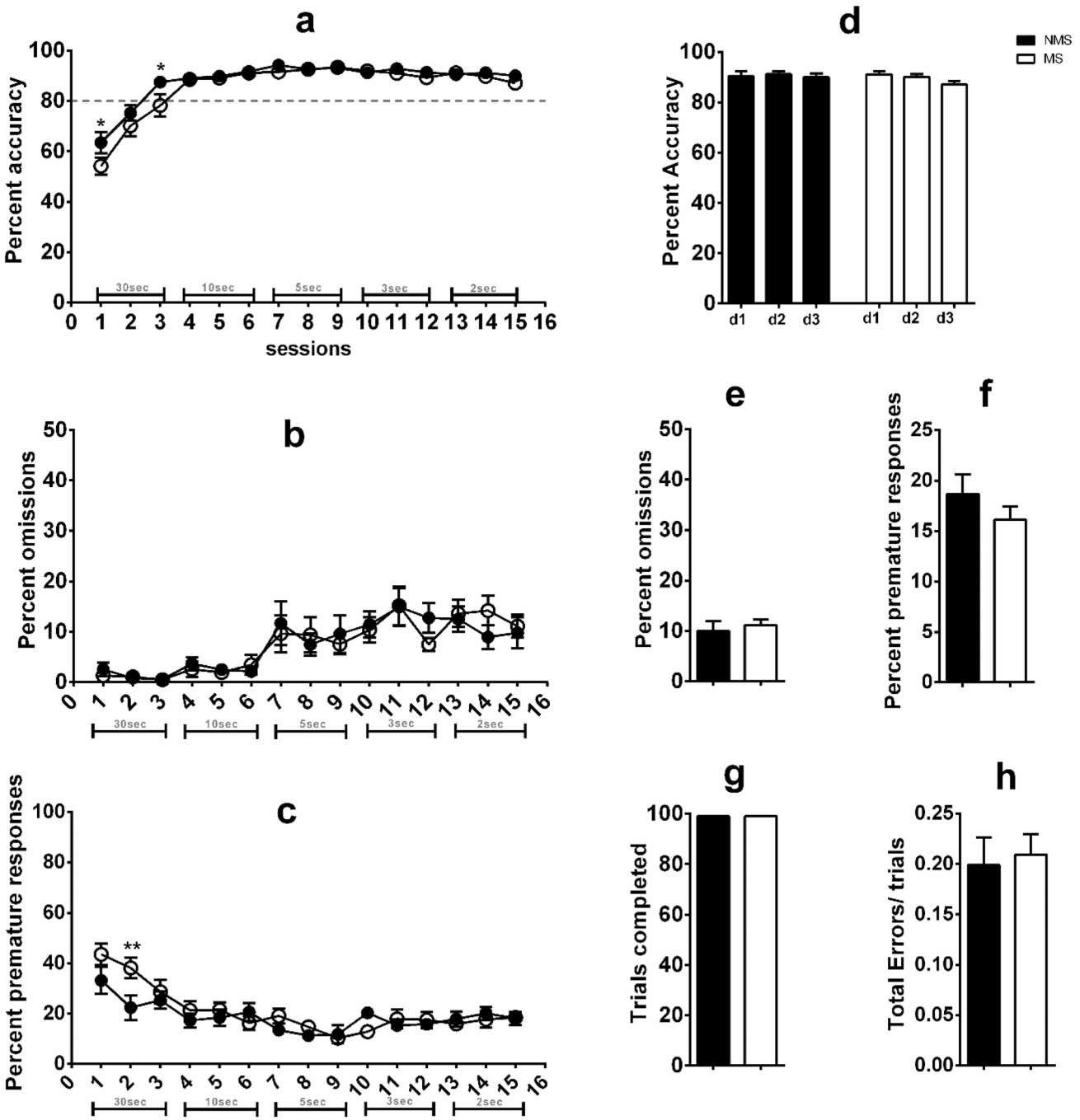

Fig. 5 Effect of maternal separation and isolation stress on 5-CSRTT performance during acquisition and baseline conditions: **a** Percent accuracy across the training performance. **b** Percent omissions across the training performance. **c** Percent premature response during the training performance. Grey coloured dotted horizontal lines in **a** represent acquisition criteria. **d** Percent accuracy performance in first 3 days of task acquisition, **e** percent omissions, **f** percent premature responses, **g** total trials completed during the baseline performance, **h** total errors performed during the entire duration of baseline performance. NMS = 13; MS = 15. Data were analysed by (**a**–**c**) two-way repeated measures ANOVA followed by Bonferroni's multiple comparison test, **d** data were analysed by one-way ANOVA followed by Bonferroni's multiple comparison test, unpaired *t* test (**e**–**h**). Data are represented as the Mean ± SEM, $*p < 0.05$, $**p < 0.01$ in comparison to NMS. *NMS* non-maternal separation stress (control) group, *MS* maternal separation stress group, *5-CSRTT* 5-choice serial reaction time task

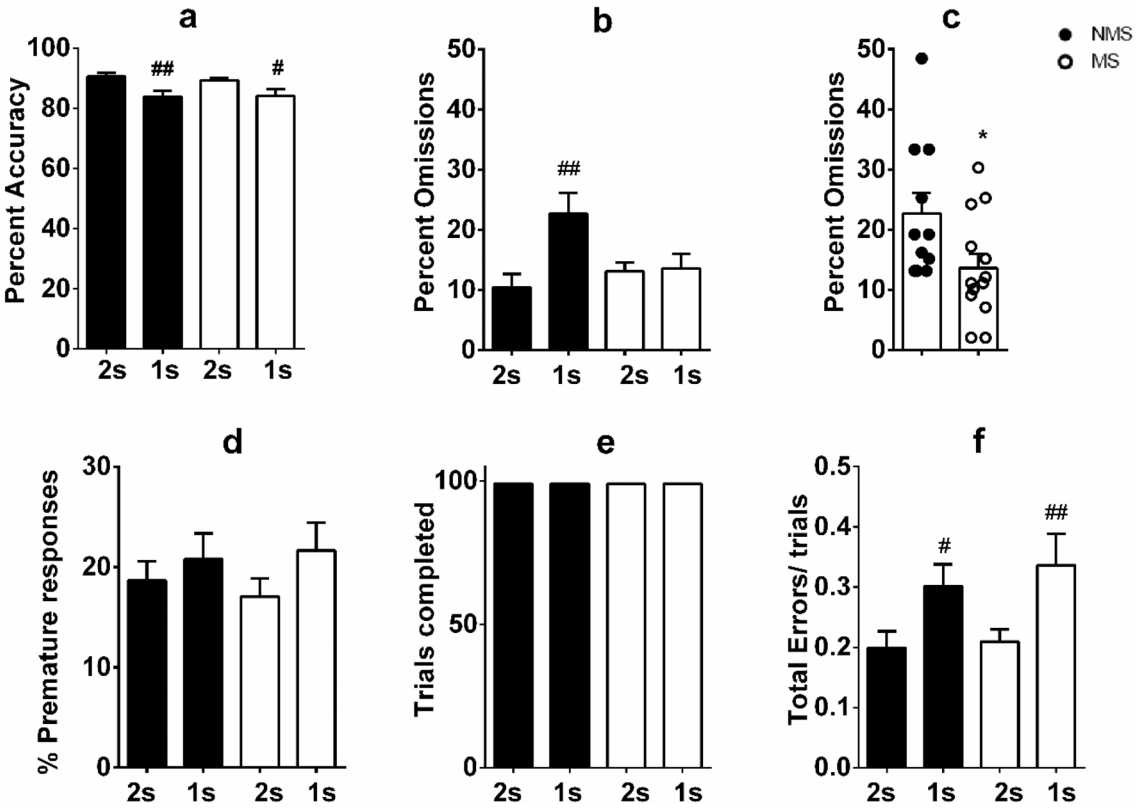

Fig. 6 Effect of MS on 5-CSRTT performance during increased attentional load: **a** percent accuracy, **b** percent omissions, **c** percent omissions between groups during increased attentional load task, **d** percent premature responses, **e** total trials completed, **f** total errors performed. NMS = 13; MS = 15. Data were analysed by unpaired *t* test (**c**); all other data were analysed by two-way ANOVA followed by Sidak's multiple comparison test. Data are represented as mean ± SEM, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ within groups, $^{*}p < 0.05$ in comparison to NMS. *NMS* non-maternal separation stress (control) group, *MS* maternal separation stress group, baseline performance is indicated as "2 s" and performance with attentional challenge is indicated as "1 s", *5-CSRTT* 5-choice serial reaction time task

Challenge had no main effect on percent premature responses ($F_{(3, 52)} = 0.846$, $p = 0.475$), and there was no main effect of MS stress ($F_{(1, 52)} = 0.0267$, $p = 0.871$) on premature responses and there was no interaction of Challenge × MS either ($F_{(1, 52)} = 0.283$, $p = 0.597$). Total trials completed were all similar in both the groups (Fig. 6e). For total trials completed, there were no main effects of Challenge ($F_{(1, 44)} = 0$, $p > 0.999$), or MS stress ($F_{(1, 44)} = 0$, $p > 0.999$) and no interaction between Challenge × MS stress ($F_{(1, 44)} = 0$, $p > 0.999$). For total errors, there was a main effect of Challenge ($F_{(1, 26)} = 17.99$, $p < 0.001$) but not of MS stress ($F_{(1, 26)} = 0.253$, $p = 0.619$). There was no interaction of MS stress × Challenge on total errors ($F_{(1, 26)} = 0.200$, $p = 0.658$). Sidak's multiple comparison test revealed an increase in total errors per trial during attentional challenge compared to baseline in NMS rats ($p = 0.031$) and in MS rats ($p = 0.004$) as seen in Fig. 6f.

Further, there was a main effect of Challenge on repetitive nosepoke responses ($F_{(1, 51)} = 10.42$, $p = 0.002$) as seen in Supp. 2a. Repetitive nosepokes were reduced during the challenge task as compared to baseline in NMS rats, i.e. within-group difference (within group; $p = 0.033$) but not in MS rats (within group; $p = 0.084$). There was no main effect of MS stress ($F_{(1, 51)} = 0.096$, $p = 0.758$) and no interaction of Challenge × MS stress ($F_{(1, 51)} = 0.140$, $p = 0.710$). For repetitive magazine entries, there were no main effects of Challenge ($F_{(1, 52)} = 0.707$, $p = 0.404$), and MS stress ($F_{(1, 52)} = 0.183$, $p = 0.670$) or interaction of MS stress × Challenge ($F_{(1, 52)} = 0$, $p = 0.994$) as seen in Supp. 2b. Additionally, for mean correct latencies, there was a main effect of Challenge ($F_{(1, 51)} = 42.18$, $p < 0.001$) but not of MS stress ($F_{(1, 51)} = 0.907$, $p = 0.345$) and the interaction Challenge × MS stress was also not significant ($F_{(1, 51)} = 0.318$, $p = 0.575$). Further Sidak's multiple comparison test showed that there were significant within-group differences in mean correct latencies for both groups (NMS: $p = 0.0003$, MS: $p < 0.0001$), but there were no significant differences between groups (Supp. 2c).

Further, two-way ANOVA revealed that Challenge had no main effect on either mean incorrect latencies ($F_{(1, 51)} = 1.219$, $p = 0.275$) as in Supp. 2d or in mean reward latencies ($F_{(1, 50)} = 0.118$, $p = 0.733$) as in Supp. 2e.

Similarly, there was no main effect of MS stress on mean incorrect latencies ($F_{(1, 51)}$ = 0.045, p = 0.832) and mean reward latencies ($F_{(1, 50)}$ = 2.762, p = 0.103). Finally, there were no interaction between the two variables for mean incorrect latencies ($F_{(1, 51)}$ = 0.581, p = 0.449) and mean reward latencies ($F_{(1, 50)}$ = 0.673, p = 0.416).

Overall, attentional challenge task provokes error making as evident in NMS rats but MS stress exposure may lead to better cognitive control, while not affecting motivation and perseverative behaviours.

Behavioural inhibition challenge with random inter-trial interval (5, 10 and 15 s ITI)

As a challenge to behavioural inhibition abilities, the NMS and MS rats were subjected to a test task consisting of trials with 5 s, 10 s and 15 s ITIs pseudo-randomly presented over 100 trials. This random ITI task was performed with 2 s SD that was used at baseline. This challenge task enabled us to assess the impulsive control as the random variable ITIs were presented for the first time to these rats.

Two-way ANOVA revealed that for percent accuracy (Fig. 7a), there were no main effects of vITI challenge ($F_{(1, 43)}$ = 0.916, p = 0.344) or MS stress ($F_{(1, 43)}$ = 0.202, p = 0.654). Also there was no interaction of MS stress × vITI challenge ($F_{(1, 43)}$ = 0.033, p = 0.856). For percent omissions, there was a main effect of vITI challenge session ($F_{(1, 43)}$ = 9.40, p = 0.004), but no main effect of MS stress ($F_{(1, 43)}$ = 0.014, p = 0.906) and no main interaction between MS stress × vITI challenge ($F_{(1, 43)}$ = 1.722, p = 0.196). Further Sidak's multiple comparison test revealed that there was a decrease in percent omissions in MS rats during vITI challenge session (Fig. 7b) as compared to baseline (within group; p = 0.005), whereas NMS rats did not show this difference (within group; p = 0.415).

For percent premature responses, there was a main effect of vITI challenge ($F_{(1, 43)}$ = 35.24, p < 0.001), but no main effect of MS stress ($F_{(1, 43)}$ = 1.553, p = 0.219) or

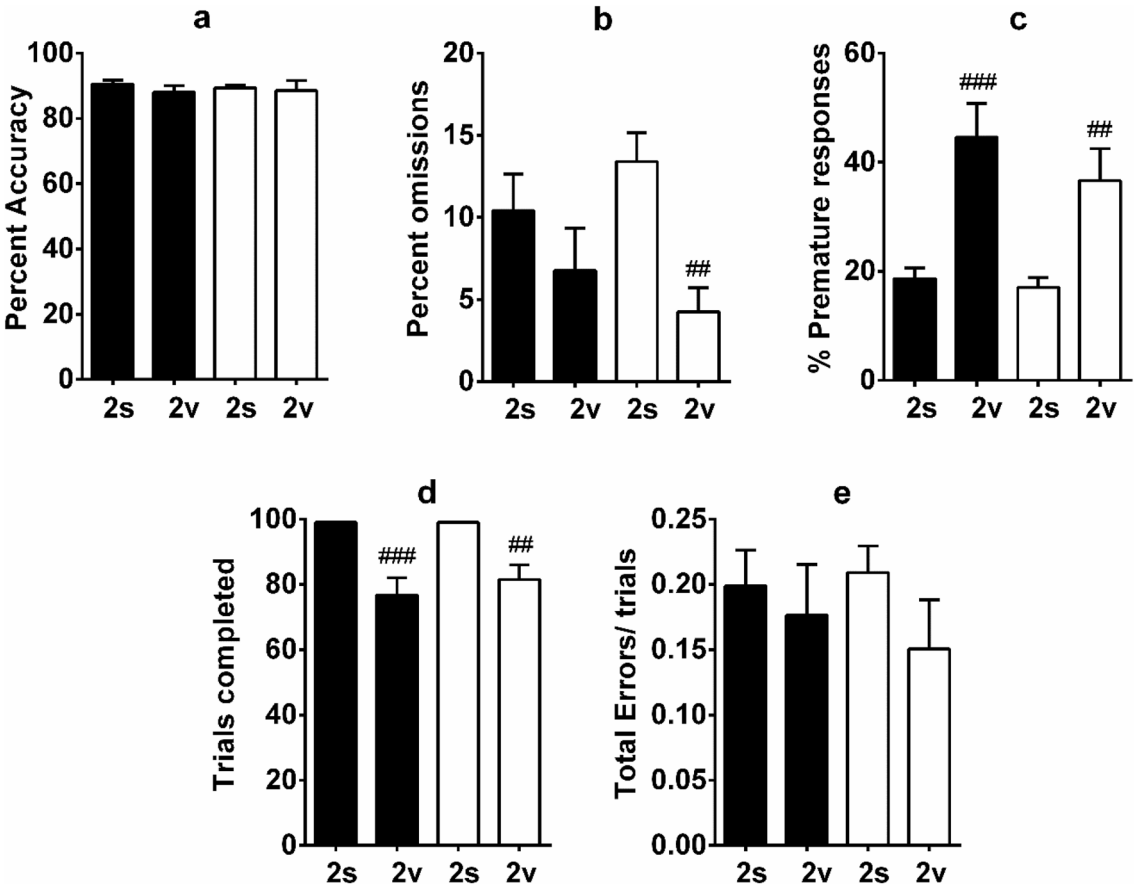

Fig. 7 Effect of MS on 5-CSRTT performance during behavioural inhibition challenge: **a** percent accuracy, **b** percent omissions, **c** percent premature responses, **d** total trials completed, **e** total errors performed. The data are presented as comparison between baseline and vITI performance for both NMS and MS groups, respectively. NMS = 9; MS = 11. Data were analysed by two-way ANOVA followed by Sidak's multiple comparison test. Data are represented as mean ± SEM. $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$ within-group comparisons. *NMS* non-maternal separation stress (control) group, *MS* maternal separation stress group; baseline performance is indicated as "2 s" and performance with vITI challenge is indicated as "2v", *5-CSRTT* 5-choice serial reaction time task

interaction of MS stress × vITI challenge ($F_{(1, 43)} = 0.682$, $p = 0.414$). Further Sidak's multiple comparison test indicated that the vITI challenge caused increased premature responses (Fig. 7c) in both NMS ($p < 0.001$) and MS groups ($p = 0.001$) but there were no group differences. Two-way ANOVA revealed that for total trials completed (Fig. 7d), there was a main effect of vITI challenge session ($F_{(1, 35)} = 34.32$, $p < 0.001$), but not of MS stress ($F_{(1, 35)} = 0.5053$, $p = 0.4819$) and there was no interaction of MS stress × vITI challenge ($F_{(1, 35)} = 0.505$, $p = 0.4819$). Further Sidak's multiple comparison test indicated that vITI challenge caused reduction (as compared to baseline) in total trials completed in both NMS ($p < 0.001$) and MS groups ($p = 0.001$) but there were no group differences. For total errors per trials in the vITI challenge task (Fig. 7e), there were no main or interaction effects (vITI challenge: $F_{(1, 43)} = 1.810$, $p = 0.185$; MS stress: $F_{(1, 43)} = 0.065$, $p = 0.799$; MS stress × vITI challenge: $F_{(1, 43)} = 0.358$, $p = 0.553$). Further Sidak's multiple comparison test showed that there was no within-group differences (NMS: $p = 0.8484$, MS: $p = 0.3001$) and between-group differences (NMS: $p = 0.9555$, MS: $p = 0.8258$) in total errors in this vITI challenge task as in Fig. 7e.

For mean correct latencies (Supp. 3a), there was a main effect of vITI challenge ($F_{(1, 36)} = 236.2$, $p < 0.001$), but no main effect of MS stress ($F_{(1, 36)} = 0.019$, $p = 0.892$) or interaction of vITI challenge × MS stress ($F_{(1, 36)} = 0.201$, $p = 0.657$). Both groups had reduced mean correct latency (NMS: $p < 0.001$, MS: $p < 0.001$) but there were no group differences.

Similarly, for mean incorrect latencies (Supp. 3b), there was a main effect of vITI challenge ($F_{(1, 36)} = 45.27$, $p < 0.001$) but no main effect of MS stress ($F_{(1, 36)} = 0.069$, $p = 0.794$) or interaction of vITI challenge × MS stress ($F_{(1, 36)} = 0.043$, $p = 0.837$). Further Sidak's multiple comparison test showed that both groups had reduced mean incorrect latencies (NMS: $p < 0.001$, MS: $p < 0.001$), but there was no between-group differences in baseline and vITI task (NMS: $p = 0.892$, MS: $p = 0.999$). For mean reward latencies (Supp. 3c), there was a main effect of vITI challenge ($F_{(1, 36)} = 269.3$, $p < 0.001$) but no main effect of MS stress ($F_{(1, 36)} = 1.831$, $p = 0.184$) or interaction of vITI challenge × MS stress ($F_{(1, 36)} = 1.236$, $p = 0.273$). Further Sidak's multiple comparison test showed that both groups had reduction in mean reward latency (NMS: $p < 0.001$, MS: $p < 0.001$) but there was no between-group differences in baseline and vITI task (NMS: $p = 0.061$, MS: $p = 0.987$).

The vITI challenge session had no main effect on repetitive nosepoke responses ($F_{(1, 34)} = 2.584$, $p = 0.112$) as in Supp. 3d. There was also no main effect of MS stress on repetitive nosepoke responses ($F_{(1, 34)} = 2.433$, $p = 0.128$) or interaction effect of vITI challenge × MS stress ($F_{(1, 34)} = 0.793$, $p = 0.379$). Further Sidak's multiple comparison test showed that there was no significant within-group difference in both NMS and MS rats in repetitive nosepoke responses (NMS: $p = 0.1502$, MS: $p = 0.8591$) and also there was no significant difference between-group comparison in vITI challenge task (NMS: $p = 0.0568$, MS: $p = 0.9065$) as in S3d.

In addition, for repetitive magazine entries (Fig. 8), there was no main effect of vITI challenge task ($F_{(1, 36)} = 0.898$, $p = 0.350$) but there was a main effect of MS stress ($F_{(1, 36)} = 28.43$, $p < 0.001$) and an interaction of MS stress × vITI challenge ($F_{(1, 36)} = 13.05$, $p < 0.001$). Further Sidak's multiple comparison test revealed increased repetitive nosepoke responses by MS rats ($p = 0.005$) but not by NMS rats ($p = 0.136$) leading to group differences in terms of repetitive magazine entries in the vITI challenge task ($p < 0.001$).

Discussion

Our results indicate that MS had both positive and negative influence on affective and cognitive functions. We found that MS moderately enhanced attentional abilities and improved spatial learning in radial arm maze. On the other hand, MS led to social novelty impairments, heightened anxiety and increased compulsive features.

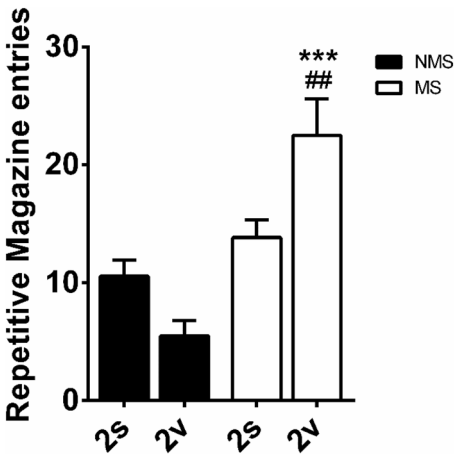

Fig. 8 Effect of MS on 5-CSRTT perseveration during behavioural inhibition challenge: repetitive magazine entries between NMS and MS groups. The data are presented as comparison between baseline and vITI performance for both NMS and MS groups, respectively. NMS = 6; MS = 6. Data were analysed by two-way ANOVA followed by Sidak's multiple comparison test and data are represented as mean ± SEM, $^{***}p < 0.001$ between group, $^{\#\#}p < 0.01$ within group. *NMS* non-maternal separation stress group (control group), *MS* maternal separation stress group. Baseline performance is indicated as "2 s" and performance with vITI challenge is indicated as "2v"

Early maternal separation stress increased anxiety-like behaviour and hampers social behaviour

Anxiety has distinctive impact on cognitive performance (Denkova et al., 2010; Hu et al. 2012; Robinson et al. 2012, 2013). In the present study, we found that maternal separation and isolation stress caused increased anxiety as found in earlier studies (Dayalan Sampath et al. 2010; Heim and Nemeroff 1999; Huot et al. 2001; Kalinichev et al. 2002; Salm et al. 2004; Wigger and Neumann 1999). In addition, our recent study showed that maternal separation and isolation stress enhanced fear memory and impaired fear extinction memory in the young adulthood (Mishra et al. 2019). Even though anxiety can interfere with cognitive performance, it could also facilitate cognitive information processing in some contexts (Robinson et al. 2013).

Accordingly, it was found that enhanced anxiety due to MS stress has affected social novelty behaviour, while it did not alter the social motivation or sociability. Interestingly, while one study has reported that MS did not alter the social behaviour in mice (Tsuda et al. 2011), and another study observed enhanced social behaviour after MS stress (Starr-Phillips and Beery 2014). Nevertheless, many studies have demonstrated that MS impairs social behaviour (Franklin et al. 2011; Yu et al. 2013). However, these differences in effects of MS on social behaviour may be attributed to the variation in maternal care on reunion of pups after MS stress (Beery and Kaufer 2015) and duration of MS procedure. Further understanding of the neural circuit mechanisms may also explain how early experiences influence the social behaviour development and related disorders.

MS rats showed better spatial learning in partially baited radial arm maze test than NMS rats

Several studies have reported that MS stress has induced behavioural deficits such as impaired spatial learning and memory (Barha et al. 2007; Bath et al. 2017; Kosten et al. 2012; Naninck et al. 2015; Wang et al. 2011). However, the present study has observed increased spatial memory in MS rats as compared to control rats. MS rats were able to achieve the learning criteria of 80% correct choice in 8 days of training whereas control rats required 13 days of training in partially baited radial arm maze task. This indicates that there is a gradual building up of stress-induced enhancement in spatial learning abilities.

This supports our earlier observations that MS stress caused increased hippocampal volume (unpublished observations of Dayalan Sampath). The increased hippocampal volume is associated with increased performance in the hippocampus mediated memory tasks (Krugers et al. 2017). In contrast, decreased hippocampal volume is associated with reduced spatial memory (Bremner and Narayan 1998; Guderian et al. 2015; Rahman et al. 2016).

MS rats were better than NMS rats in stimulus detection but showed enhanced reward-seeking behaviour with compulsive features during 5-CSRTT testing

We explored the detrimental effects of MS on cognitive functions such as attention and response control using 5-CSRTT—a standard task that is widely used to assess these functions in rodents. MS rats showed mild task acquisition impairments (lower response accuracy at the first level of training i.e. SD 30 s) but we did not find group differences in any of the subsequent training stages. As MS and NMS rats showed similar performance in all 5-CSRTT parameters at baseline (SD 2 s), we infer that MS-induced anxiety might not have affected attention and response control aspects of cognitive functioning at the baseline level of the task.

As expected, NMS rats showed decreased performance in shorter stimulus duration (an attentional challenge) session as compared to baseline session (Amitai and Markou 2011). Surprisingly, MS rats did not show these performance decrements under the shorter stimulus condition. Moreover, MS rats had significantly lower omissions than NMS rats during shorter stimulus condition. Overall, MS rats showed better attentional and stimulus detection abilities than the NMS rats.

A recent study found that MS on PND 3 for 24 h did not alter attentional performance in 5 CSRTT at baseline level as well as with shortened stimulus duration (Kentrop et al. 2016). However, this study had used a single-day (24 h) maternal separation protocol unlike our study where we have used 6 h of maternal separation (PND 4–14). The short deprivation used by Kentrop et al. might not have provided sufficient impact to alter attentional processing in 5-CSRTT. The findings of the current study are in accordance with those of Boutros et al. (2017), where MS for 3 h from PND 1–14 enhanced attentional performance during task challenge sessions (with increased attentional load). It is noteworthy that Boutros et al. (2017) had also reported that rats exposed to MS displayed improved attentional performance under baseline conditions (Boutros et al. 2017). It should be noted that the baseline stimulus duration was 1 s for Boutros et al. (2017) whereas the present study has used 2 s as baseline stimulus duration and 1 s as the increased attention load challenge. The easier baseline stimulus condition in our study (as compared to Boutros et al. 2017) is likely to be the reason for the absence of group differences at baseline in our findings.

Our vITI challenge enabled assessment of both aspects of inhibitory control i.e. impulsivity and compulsivity in MS and NMS rats (Chudasama et al. 2003). The vITI challenge

session revealed that MS rats did not have deficits associated with impulsive behaviour, as there was an increase in premature responses in both groups as compared to the baseline performance but there were no group differences.

On the other hand, MS rats made significantly higher additional magazine entries after the pellet collection during the vITI challenge, indicating increased perseverative responses in these rats (Dalley et al. 2011). Perseverative responses are the measure of "compulsive behaviour" in which rats continue to respond repeatedly, either at the aperture where responding has just earned reward or in food magazine or at the other locations during 5-CSRTT (Bari et al. 2008; Brydges et al. 2015; Leeman and Potenza 2012; Morton and Munakata 2002; Robbins 2002). Previous studies had also reported compulsive behaviour in rats with early life stress during both baseline and testing stages of 5-CSRTT (Tzanoulinou et al. 2016). Brydges et al. (2015) showed that MS (particularly on PND 9) leads to perseveration in both male and female rats (Brydges et al. 2015) in delay discounting task. Our study involved only male Wistar rats and MS procedure was from PND4 to PND14. Further study with both male and female rats using our extensive MS protocol might reveal some interesting gender dependent changes in 5-CSRTT parameters.

It is noteworthy that this compulsive behaviour in MS rats was not observed during 5-CSRTT training and the challenge session with shorter stimulus duration. This is most likely due to the fact that in vITI sessions, two-third of the ITIs were longer (10 s and 15 s) than the standard ITI (5 s) used in other task sessions. Therefore, the rats had to wait for a longer time before the stimulus onset, during vITI sessions as compared to other sessions. This longer waiting time might have provoked perseverative behaviour in MS rats (Brydges et al. 2015). In 5-CSRTT, longer waiting period is also commonly used as a task manipulation to provoke motor impulsivity (leading to premature responses) in rats. However, in the present study, MS rats demonstrated only compulsive behaviour without having any signs of impulsivity in them during the longer ITI trials. This functional dissociation might be explained by involvement of a specific neural circuitry underlying the MS-induced behavioural changes found in our study. Previous studies in rats with ventral prefrontal cortex (vPFC) lesions had also shown different neural substrates for impulsivity and compulsivity in 5-CSRTT. For example, orbitofrontal cortex (OFC) was shown to be involved in perseverative tendencies whereas infralimbic cortex (IL) was responsible for 'impulsive' premature responding (Chudasama et al. 2003). Additionally, both impulsive and compulsive behaviours are known to depend on the specific neuromodulation of mPFC. 5-HT_{1A} receptor activation in mPFC has been shown to enhance perseverative behaviour but not impulsiveness (Carli et al. 2006).

Since perseverative behaviour in MS rats was limited to making multiple entries to reward magazine and was not generalized (i.e. they did not make repeated entries to the nose poke holes), we consider that the behaviour can be categorized as enhanced reward-seeking behaviour in MS rats that leads to compulsive responses in them. Therefore, our data predict the major involvement of nucleus accumbens in this kind of perseveration on the reward magazine in MS rats (Christakou et al. 2004). Overall, it can be suggested that increased compulsive features seen in MS rats could be because of altered fronto-striatal circuit in these rats, but this need to be further confirmed by direct studies. Further, Compulsive behaviour indicates inability to alter behaviour in response to changing situational demands and is often taken as an index of cognitive inflexibility (Chamberlain et al. 2006; Dalley et al. 2004). Thus, findings of the present study suggest that early MS-induced anxiety not only enhances the compulsive behaviour but may also predict cognitive inflexibility. Increased perseveration may contribute to the development of substance abuse and addictions of drugs and gambling (Brydges et al. 2015).

We also evidenced another form of cognitive inflexibility in social novelty behaviour, i.e. social cognitive inflexibility, previous studies also suggested that maternal separation and isolation stress alter the social interaction behaviour (Jia et al. 2009; Sandi and Haller 2015; Wei et al. 2013). One cause could be due to overlapping of the social brain network (Rennie et al. 2013; Sandi and Haller 2015) with the default cognitive network (Amft et al. 2015; Hsu et al. 2016). Therefore, when MS stress alters stress response system, it may affect both cognitive and social behaviour (Chen and Baram 2016). Further studies are warranted to understand and map the overlapping brain network of cognition and social behaviour to unravel the neuro-circuitry behind such deficits.

Conclusion

The findings from the present study provide a more nuanced understanding of early life stress on cognitive and emotional outcomes later in adulthood. Our findings demonstrate that how maternal care disruption in critical early postnatal period can have differential effects on cognitive and affective functions. MS enhanced attentional abilities and improved spatial learning and memory. On the other hand, MS led to social inflexibility, heightened anxiety and increased reward-seeking behaviour. Overall, our study highlights the impact of early life stressors spanning affective and cognitive domains. Further studies are warranted to develop training strategies in people with history of early life challenges that enhance the positive effects (higher cognitive functioning)

and counter the negative effects (heightened affective processing), to facilitate a better quality of life.

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Compliance with ethical standards

Conflict of interest The authors (M. Y. K., K. A., B. M. K., R. S. M, and T. R. L.) have no conflicts of interests to declare.

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