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The stop null mice model for schizophrenia displays [corrected] cognitive and social deficits partly alleviated by neuroleptics

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Abstract

Recently, evidence has been accumulated that schizophrenia can arise from primary synaptic defects involving structural proteins and especially microtubule associated protein. Previous experiments have demonstrated that STOP gene deletion in mice leads to a phenotype mimicking some aspects of positive symptoms classically observed in schizophrenic patients. Here we have assessed social and cognitive functions in STOP null mice. Compared to wild-type mice, STOP null mice exhibited deficit in the non-aggressive component of social recognition, in short term working memory and in social and spatial learning, which, as in human schizophrenia, were poorly sensitive to a long term treatment with typical neuroleptics. Since, social and cognitive dysfunction have consistently been considered as central features of schizophrenia, we proposed that STOP null mice may provide a useful model to understand the neurobiological correlates of social and cognitive defects in schizophrenia and to develop treatments that better target these symptoms.

MESH Keywords Animals ; Antipsychotic Agents ; pharmacology ; Cognition ; physiology ; Feeding Behavior ; physiology ; Interpersonal Relations ; Learning ; physiology ; Male ; Maze Learning ; physiology ; Mice ; Mice, Knockout ; Microtubule-Associated Proteins ; genetics ; physiology ; Psychomotor Performance ; physiology ; Recognition (Psychology) ; physiology ; Schizophrenia ; genetics ; Schizophrenic Psychology ; Smell ; physiology ; Social Behavior ; Space Perception ; physiology

Author Keywords schizophrenia, STOP null mice, cognitive defects, learning, memory, social interactions

Introduction

Mohamed et Thierry : Pb entre symptômes cognitifs qui réferent à la désorganisation du comportement et de la pensée et « cognitive impairment ou dysfunction » tel qu'on le définit.

Schizophrenia is one of the most disabling and emotionally devastating illnesses of the human brain. Pathology is characterized by three broad types of symptoms, including psychotic symptoms, negative symptoms, and cognitive impairments. Although neuroleptics (NL) are very efficient to improve psychotic symptoms (Ereshefsky et al., 1990 ; Mueser and McGurk, 2004), there is no consensus that any of the currently available NL alleviate the negative symptoms and the debilitating cognitive dysfunction associated with schizophrenia (Sergi et al., 2007 ; Sernyak et al., 2003 ; Peuskens et al., 2005) suggesting different neuronal substrates for these symptoms (Brown and Pluck, 2000 ; Tamminga, 2006 ; Burns, 2006). Negative symptoms are deficit states in which basic emotional and behavioral processes are diminished or absent. Common negative symptoms include blunted affect, anhedonia and social withdrawal. In schizophrenia, cognitive dysfunction is not global and generalized but rather is specific and selective, including problems with attention and perception, problem solving, short- and long-term memory and in particular working memory. Of the many clinical features of schizophrenia, social dysfunction and disturbances in cognitive processes might represent the core features of the illness because they often occur prior to the first psychotic episode, persist and frequently deteriorate throughout the course of illness (Thaker and Carpenter, 2001 ; Chemerinski et al., 2002 ; Mueser and McGurk, 2004). Furthermore, social and cognitive dysfunction are strongly associated with functional impairments, including community living and work. Being able to address these deficits in a preclinical model and consequently develop drugs that better target these symptoms could lead to better outcome and better quality of life for patients.

The origin of schizophrenia is still debated, but current data favor a model in which schizophrenia arises from defects in neuronal connectivity, principally caused by synaptic alterations (Mirnics et al., 2001 ; Owen et al., 2005). Recently, the protein coded by a gene (DISC1) known to be disrupted in a familial form of schizophrenia has been characterized and shown to be involved in a variety of interactions with microtubule-related organelles or proteins, suggesting that connectivity disorders in schizophrenia can result from cytoskeletal alterations (Callicott et al., 2005 ; Morris et al., 2003).

Consistent with this hypothesis, Shimitzu et al. (2006) have found an association between schizophrenia and polymorphisms in the MAP6 gene which encodes a microtubule-associated protein. STOP (Stable Tubule Only Polypeptide) null mice generated by disrupting the MAP6 gene (Bosc et al., 1996 ; Bosc et al., 2003) satisfy this construct validity (Andrieux et al., 2002). This genetic animal model has

been already shown to display a set of defects similar to those of schizophrenia disorders. At the behavioral level, STOP null mice have been shown to display neuroleptic-sensitive behavioral abnormalities thought to simulate some aspects of positive symptoms classically observed in schizophrenic patients (Andrieux et al., 2002 ; Brun et al., 2005). These mice exhibit increased basal locomotor activity during the dark phase of the light/dark cycle associated with purposeless and disorganized activity (Andrieux et al., 2002 ; Brun et al., 2005). Additionally, STOP null mice display a supersensitivity locomotor reaction to acutely stressful situation, such as a single saline injection and exposure to novelty and an increased locomotor stimulatory effect of psychomimetic drugs such as amphetamine (Brun et al., 2005). Some of these locomotor activity defects are present in juvenile mice, whereas others appear only in adulthood mimicking thus the life long evolution of the pathology (Bégou et al., 2007). Interestingly, STOP null mice exhibit also severe perturbations of complex behaviors including impaired nesting and severe nurturing defects, anxiety-related behavior, dramatically reduced aggressive encounters, impairment in sensorimotor gating (pre-pulse inhibition-PPI), failing in object and odor discrimination and poor performance in a water-maze cued place task (Andrieux et al., 2002 ; Fradley et al., 2005 ; Powell et al., 2007 ; Bouvrais-Veret et al., 2007). These behavioral anomalies suggest that these mice could mimic some aspects of social dysfunction in schizophrenic patients and exhibit cognitive deficits in tasks that require learning and memory. Despite their complexity, these processes can be directly assessed in animals. Here, spatial working memory was tested in a Y-maze paradigm. Spatial and social learning were investigated using olfactory cues in a spatial learning olfactory guided test and a conspecific recognition test. Preliminary to learning ability assessment, as a control of STOP null mice olfactory perception skills, mice were tested in a hidden food retrieving test using familiar and palatable food. In parallel, the social functioning of STOP null mice was further characterized by measuring conspecific interactions in home-cage. Interestingly, long-term NL treatment has been shown to suppress hyperlocomotion disorders in STOP null mice (Brun et al., 2005). Because current NL treatments are known to be poorly effective on cognitive dysfunction in human (Sergi et al., 2007 ; Sernyak et al., 2003 ; Peuskens et al., 2005), as a proof of concept, we tested the effect of a long-term NL treatment on the behavior of mice in the conspecific recognition test and in the spatial learning olfactory guided test. The spatial and social learning abilities were compared in drug free and long term NL-treated wild-type (WT) and STOP null mice.

Materials and methods

Animals

Male STOP null mice (STOP−/−) and their wild-type (WT) littermates (STOP +/+) were generated as previously described (Andrieux et al., 2002). Mice were housed eight per cage in a temperature (22±1°C) controlled environment under a 12:12 light/dark cycle (light from 6:00 AM to 6:00 PM), with ad libitum access to familiar food (Harlan pellets) and water unless otherwise specified. All animals used in this study arose from the same colony (BALBc/129 Sv background). Different mice were allocated to each test unless otherwise specified. Drug free and long term neuroleptic (NL) treated animals (3- to 5-month-old, 25 to 30 g) were investigated in a random order for comparisons between genotypes. Experimenter was blind to genotype during testing. All tests took place during the light phase of the cycle between 9 and 12 AM except for spatial learning olfactory guided test conducted from 12 to 17 PM. In all experiments, animals were allowed to habituate to the testing room 1 h before the test.

Experiments were performed in accordance with French and European Economic Community guidelines for the care and use of laboratory animals.

Y-maze test

Spontaneous alternation behavior and exploratory activity were recorded in a Y-maze. The apparatus consisting of three walled arms (5 cm wide, walls: 15 cm) made of black painted wood was placed in a dark room illuminated only by an halogen lamp giving an uniform dim light in the apparatus (intensity of 10 Lux in the center of the maze). The start arm (20 cm long) and the two arms forming the Y (both 15 cm long) were radiating at an angle of 120° from each other. Without prior habituation to the apparatus, each mouse was placed into the start arm and allowed to move freely through the maze during an 8-min session. The arms were extensively cleaned with water between each animal change to avoid olfactive cues. The sequence of arm entries was manually counted from video recordings that allowed the experimenter to be out of view of the animal. A mouse was considered to have entered an arm when all four paws were positioned in the arm runway. The number of arm entries was used as an indicator of locomotor activity. An alternation was defined as entries into all three arms on consecutive choices. The alternation score (%) for each mouse was defined as the ratio of the actual number of alternations to the possible number (defined as the total number of arm entries minus two) multiplied by 100 as shown by the following equation: % Alternation = [(Number of alternations)/(Total arm entries − 2)] × 100. Mice that completed only 8 arm entries or less within 8 min were excluded from further analysis (Sakaguchi et al., 2005).

Hidden food test

Retrieving capacities of WT and STOP null mice was assessed using familiar (Harlan pellet) and unfamiliar (raisin) food. Palatability of raisin was previously tested (data not shown) in comparison with other unfamiliar food i.e. chocolate cereal (Chocopops™), honey cereal (Mielpops™) and corn flakes. When WT and STOP null mice had simultaneously free access to the different unfamiliar foods, they always ate at first the raisin. We then considered that raisin was the more palatable food between the different foods tested.

In a preliminary experiment, several days before testing, unfamiliar food (a raisin cut into pieces of 10 to 15 mg) was placed overnight in the home cages of the mice. Observations of consumption were taken to ensure that the novel food was eaten by all mice. In a hidden food test, each mouse was proposed to retrieve in a 2-trial session either familiar food or unfamiliar palatable food out of sight. Hidden food test was performed in a transparent Plexiglas arena (10cm(w) × 20cm(l) × 13cm(h)) closed with a transparent Plexiglas cover. The floor of the arena was covered with bedding (2 cm). At the beginning of each trial, familiar food (a Harlan pellet) or unfamiliar palatable food (a raisin) was hidden beneath bedding at one end of the arena (in the middle of one of the shorter sides, 10 cm apart). Different mice were allocated to find familiar and palatable food. Bedding and food were changed between each trial and mouse. A 16-h food deprivated mouse was introduced at the opposite end of the arena and the time taken for the mouse to find the hidden food was recorded. The mouse, not allowed to eat, was then promptly returned to its home cage for a 30-min inter-trial period. If food was not found, after 5 min, it was considered that the mouse failed, the test was stopped and 300 s was then allocated for that trial. In each trial, scores were expressed as the percentage of mice succeeding in finding food and as the latency (mean±SEM) to do it.

Spatial learning olfactory guided test

In this learning task, changes of mice abilities in retrieving palatable food over successive trials were assessed. This test was performed in a transparent Plexiglas arena (26 cm(w) × 41 cm(l) × 20 cm(h)) tagged with visual cues (different shaped symbols) on each wall and closed with a transparent Plexiglas cover. The floor of arena was covered with bedding (2 cm). Mice previously allocated to the hidden food test were used. The test session was conducted the day after the end of a 4-day training session. In the training session, mice were given 3 trials each day in which a piece of raisin (10–15 mg) was placed visible on top of bedding at one end of arena (in the middle of one of the shorter sides, 10 cm apart). In each trial, a mouse was introduced into the opposite end and allowed to habituate and eat for 5 min before being returned to its home cage for a 1-h inter-trial period. Between each trial and mouse, bedding and raisin were changed. At the end of the training session, WT mice exhibited a criterion of 80% of correct responses (food found under cut-off) over 3 consecutive trials. In the test session, mice were food deprivated for 6 hours before testing and were given four successive 5-min trials. The first trial (T0) was conducted with a piece of raisin visible on top of the bedding while the three other trials (T1, T2 and T3) were conducted with a piece of raisin hidden beneath 1 cm of bedding. Other conditions, including the location of raisin, the starting position of mice and the inter-trial period were the same as described in the training session. For each mouse and trial, latency to find raisin was recorded. If the piece of raisin was not found after 5 min, the test was stopped and 300 s was then allocated for that trial. Scores were expressed for each trial as the percentage of mice succeeding in finding raisin and as the latency (mean±SEM) to do it.

Conspecific recognition test

In this test, WT and STOP null mice, used as residents, were individually housed for 1 week before testing to permit establishment of a home-cage territory. Heterozygous mice, used as intruders, were housed 6 per cage and were unfamiliar of mice used as residents. Intruder mice were deeply anaesthetized by an i.p. injection of urethane (1.8 g/kg; 10 mL/kg) at least 10 min prior to the experiment. Four trials lasting for 3 min were repeated with a 12-min inter-trial period. The first trial (T1) was used to assess home-cage social interaction. In the first three trials (T1 to T3), the same anaesthetized intruder (mouse 1) was used to assess habituation. In the fourth trial (T4), a novel anaesthetized intruder (mouse 2), representing a novel challenge, was used to assess discrimination. In each trial, the intruder was placed prone at the centre of each resident home cage (10cm(w) × 20cm(l) × 13cm(h)) and the exploration activity of the resident was immediately manually recorded for 3 min. The intruder was then promptly removed. Exploration activity was measured as the time spent by the resident in sniffing the intruder animal. Sniffing is defined as olfactory exploration and close contact (<1 cm) between the resident nose or vibrissae and the body of the intruder (Hunter and Murray, 1989 ; Yamada et al., 2000).

Long term neuroleptic treatment

Long term NL treated mice received haloperidol (Haldol™ , Janssen-Cilag; 0.5 mg/kg/day) and chlorpromazine (Largactil™ , Aventis Pharma; 5 mg/kg/day) dissolved in the drinking water from weaning to the day of experiment, as previously described (Andrieux et al., 2002). Haloperidol and chlorpromazine are antipsychotic drugs, widely used in the treatment of schizophrenia symptoms. Their beneficial effects have been attributed to their ability to block dopaminergic transmission thanks to their dopaminergic D_2 receptor antagonist properties. Wild-type and STOP null mice long term treated with NL were compared to corresponding free drug animals in the conspecific recognition test and in the spatial learning olfactory guided test.

Statistical analysis

In the Y-maze test, the percentage of alternations and the total number of arms entered were expressed as mean ± SEM and comparisons between genotypes were analyzed with an unpaired Student's t -test.

In the hidden food test, the latency to find the food was expressed as the mean ± SEM and data were analyzed with a two-way ANOVA, with genotype as main factor and trials as the repeated measures. An unpaired Student's t -test was used for comparison between genotypes for each trial. A paired Student's t -test was used for comparison between trials for each genotype. The distribution of mice finding the food was expressed as the percentage of success and a chi-square test was used to compare genotypes, at each trial.

In the spatial learning olfactory guided test, the latency to find the food was expressed as the mean ± SEM and data were analyzed with a three-way ANOVA, with genotype and treatment as main factors and trials as the repeated measures. Post-hoc Newman-Keuls comparisons were used to assess differences between trials within each genotype and differences between genotypes for each trial were assessed with an unpaired Student's t -test. The distribution of mice finding the raisin was expressed as the percentage of success. A chi-square test was used to compare genotypes, at each trial.

In the conspecific recognition test, the time spent exploring the anaesthetized mouse at each trial was expressed as the mean ± SEM. Data were analyzed as described in the spatial learning olfactory guided test.

Results

Y-maze test

Spatial working memory was assessed by testing the spontaneous alternation performance in a Y-maze. In STOP null mice, the percentage of spontaneous alternation (27.0 ± 3.6 %) was significantly lower ($p<0.01$, Student's t -test) than that of WT mice (46.3 ± 3.4 %) (Fig 1a). The total number of arm entries did not change between genotypes (32.4 ± 3.5 and 32.0 ± 4.7 for WT and STOP null mice, respectively, $p>0.05$, Student's t -test) (Fig 1b). These results suggest that STOP null mice exhibit impairment in working memory.

Hidden food test

Hidden food test was conducted to eliminate major olfactory impairments in STOP null mice. After a 16 h-food deprivation, each mouse was proposed to find in a 2-trial session either familiar food (a Harlan pellet) or unfamiliar palatable food (a raisin), hidden beneath the bedding. For each sort of food, the performance was expressed as the percentage of mice finding food and the latency to do it.

When familiar food was hidden, the percentage of mice succeeding to find food were similar between WT and STOP null mice (n= 8/genotype, trial 1, 100 and 87.5 % and trial 2, 100 and 75 %, respectively) ($p>0.05$, trial 1 chi-square=1.07, df=1 and trial 2 chi-square= 2.29, df=1). When latency was considered, a significant effect of genotype ($F(1,14)=6.15$, $p<0.05$) but not of trial was identified. The genotype x trial interaction was not significant ($F(1,14)=3.38$, $p>0.05$). Compared to WT mice, the latency to find hidden familiar food was higher in STOP null mice in the second trial (63.9 ± 16.2 and 186.3 ± 34.9 s respectively) ($p<0.01$, Student's t -test) but not in the first trial (72.3 ± 22.0 s and 128.4 ± 35.7 s, respectively) ($p>0.05$, Student's t -test).

When the test was performed with palatable food, both genotypes were able to find hidden raisin. In WT and STOP null mice, the number of mice finding raisin under the cut-off increased over trials. Compared to WT mice, the percentage of STOP null mice finding raisin was significantly lower in first trial ($p<0.05$, chi-square=4.00, df=1), but not in the second trial ($p>0.05$, chi-square=2.25, df=1) (Fig 2a). When latency to find hidden raisin was considered, a significant effect of genotype ($F(1,16)=16.64$, $p<0.001$) and trial ($F(1,16)=27.57$, $p<0.001$) was identified while the genotype x trial interaction was not significant ($F(1.16)=0.01$, $p>0.05$). Over trials, the latency to find hidden raisin was decreased in both WT ($p<0.01$, Student's t -test) and STOP null mice ($p<0.05$, Student's t -test). Compared to WT mice, the latency to find hidden raisin was higher in STOP null mice in both trials ($p<0.01$, Student's t -test) (Fig 2b). Totally, the results suggest that in a second trial both genotypes succeed in finding hidden palatable food to the same extend under cut-off, but compared to WT mice, STOP null mice are slower to do it.

Spatial learning olfactory guided test

Spatial learning was addressed as the ability of mice to locate hidden palatable food as rapidly as they located the visible one. Mice were tested on four consecutive trials (T0 to T3) to find a piece of raisin either visible (T0) or hidden beneath the bedding (T1 to T3).

When latency was considered, a significant main effect of genotype ($F(1,35)=19.99$, $p<0.001$) and trial ($F(3,105)=17.24$, $p<0.001$) but not treatment ($F(1,35)=0.06$, $p>0.05$) was identified. The genotype x trial interaction ($F(3,105)=3.47$, $p<0.05$) was significant but not the genotype x treatment interaction ($F(1,35)=0.02$, $p>0.05$).

In drug free animals, ANOVA with repeated measures revealed that the latency to find the piece of raisin was different over trials ($F(3,51)=5.23$, $p<0.01$) and between genotypes ($F(1,17)=5.83$, $p<0.05$). When raisin was visible (T0), the number of mice succeeding and

the latency to find food were not significantly different between drug free genotypes ($p>0.05$, chi-square=1.31, df=1; $p>0.05$, Student's t -test respectively) (Figs 3a, 3b). When raisin was hidden, in T1, the latency of WT mice to find food was deteriorated compared to visible condition (T1 compared to T0, $p<0.05$, Newman-Keuls comparison). Over trials, drug free WT mice showed a decrease in latency to find hidden food (T3 compared to T1, $p<0.05$, Newman-Keuls comparison) (Fig 3b) parallel to an increase in mice succeeding (Fig 3a), the latency reaching after 3 trials a value similar to that recorded in visible condition (T3 compared to T0, $p>0.05$, Newman-Keuls comparison) (Figs 3b). In contrast, the responses of drug free STOP null mice did not significantly change over trials ($p>0.05$, Newman-Keuls comparisons) (Fig 3b). Compared to WT mice, for both T2 and T3, the latency to find food remained significantly higher ($p<0.01$, Student's t -test) (Fig 3b) and the percentage of mice succeeding lower in STOP null mice ($p<0.01$, chi-square=6.74 and 9.02 on T2 and T3, respectively, df=1) (Fig 3a).

In NL treated animals, ANOVA with repeated measures revealed that latency to find the piece of raisin was different over trials ($F(3,54)=12.45$, $p<0.001$) and between genotypes ($F(1,18)=23.95$, $p<0.001$). When raisin was visible (T0), in STOP null mice, the percentage of mice succeeding was lower ($p<0.05$ and chi-square=4.09, df=1) compared to WT mice while latency to find food was higher ($p<0.05$, Student's t -test) (Figs 3c, 3d). When raisin was hidden, changes in performance, over trials, of both NL treated WT and STOP null mice were similar to those described for drug free corresponding mice. Over trials, latency to find raisin remained significantly higher in STOP null mice compared to WT mice ($p<0.05$, Student's t -test on T1 and T2, $p<0.001$, Student's t -test on T3) (Fig 3d). The percentage of NL treated STOP null mice finding raisin was lower than that of WT animals ($p<0.05$, chi-square=5.09 on T1 and $p<0.01$, chi-square=7.1 and 10.91 on T2 and T3, df=1) (Fig 3c).

These results suggest that STOP null mice are not able to learn the location of a palatable food over successive trials and that this deficit is not improved by long term NL treatment.

Conspecific recognition test

Social interactions and recognition have been addressed, as the sniffing investigation displayed in response to repeated presentations (4 trials) of anaesthetized intruder mice. The same mouse was used as intruder in the first three trials (T1 to T3) and a new one in the fourth trial (T4). A significant main effect of genotype ($F(1,28)=4.3$, $p<0.05$), trial ($F(3,84)=16.08$, $p<0.001$) and treatment ($F(1,28)=4.91$, $p<0.05$) was identified. The genotype x trial interaction ($F(3,84)=4.79$, $p<0.01$) was significant but not the genotype x treatment interaction ($F(1,28)=0.1$, $p>0.05$).

In drug free WT mice, ANOVA with repeated measures revealed that the duration of sniffing was different over trials ($F(3,21)=28.06$, $p<0.001$). Over trials, data showed a characteristic decline in the time spent investigating the first intruder (T2 and T3 compared to T0, $p<0.05$, Newman-Keuls comparisons) and a significant recovery following the introduction of the second one (T4 compared to T3, $p<0.05$, Newman-Keuls comparison) (Fig 4a). Conversely, drug free STOP null mice did not exhibit different durations of sniffing over trials ($F(3,21)=0.7$, $p>0.05$). The time they spent exploring the anaesthetized mouse on T1 was dramatically lower than that of drug free WT mice ($p<0.01$, Student's t -test) (Fig 4a). These results suggest that STOP null mice exhibit deficit in social exploration, do not habituate their response to the repetitive presentations of the first intruder and do not discriminate a new intruder.

In long term NL treated WT mice, ANOVA with repeated measures did not reveal difference in sniffing duration over trials ($F(3,21)=2.891$, $p>0.05$) suggesting a less pronounced profile of activity compared to drug free WT animals (Fig 4b). In contrast, treated STOP null mice exhibited different durations of sniffing over trials ($F(3,21)=3.93$, $p<0.05$, ANOVA with repeated measures). A decline in time spent in exploring the first intruder (T2 and T3 compared to T1, $p<0.05$, Newman-Keuls comparisons) was observed while there was no significant recovery following the introduction of the second intruder (T4 compared to T3, $p>0.05$, Newman-Keuls comparison) (Fig 4b). After long term NL treatment, the sniffing duration displayed by treated WT mice on T1 was very close to that of corresponding drug free WT mice. In T1, the difference between treated WT and STOP null mice was erased ($p>0.05$, Student's t -test) suggesting an improvement of social exploration in treated STOP null mice (Fig 4b).

Discussion

The purpose of the present study was to investigate whether STOP null mice demonstrate phenotypic difference across a variety of cognitive and social interaction paradigms which access processes similar to those known to be disrupted in schizophrenia, including home-cage social interaction, working memory, spatial and social learning. The effect of NL was further tested in learning paradigms.

STOP null mice exhibited normal olfaction capacities

To assess olfactory perception in STOP null mice, we examined their performance in a hidden food retrieving test. Mildly food deprived STOP null mice were able to locate hidden food (familiar and palatable) indicating that they exhibit no gross olfactory

impairment. These results, in agreement with previous ones showing no disturbance in olfactory bulb anatomy (Andrieux et al., 2002 ; Couegnas et al., 2007), allowed us to use olfactory cues for testing social interaction, memory and learning capacities in STOP null mice (Eichenbaum, 1998 ; Slotnick, 2001).

Notably, STOP null mice spent more time than WT mice to find the hidden food (familiar or unfamiliar). These results could argue for a lack of food palatability in STOP null mice which could be related to a deficit in motivation in these mice.

STOP null mice exhibited deficits in home-cage social interaction

In schizophrenia, social dysfunction is linked to emotional flattening, social isolation, and interpersonal oddity. Social interaction measures in rodents are directly analogous to social interaction measures in humans. Social interactions in rats and mice have been described with an aggressive and a non-aggressive but active components. Aggressive social interactions can be assessed by biting, fighting and vocalization while sniffing, nosing, following, mounting and mutual grooming can be considered as non-aggressive interactions (Yamada et al., 2000). From previous study, STOP null mice clearly exhibit a reduced aggressive and non-aggressive response in the presence of a male intruder (Andrieux et al., 2002). In such conditions, the low aggressive response of STOP null mice could favor the intruder to develop attacks which in turn could prevent non-aggressive response from STOP null mice.

In this study, the non-aggressive component of social interactions was addressed in a conspecific recognition test, as the sniffing investigation displayed in response to a first presentation of an intruder, the aggressive component being largely reduced by using an anaesthetized animal as intruder (Yamada et al., 2000). Social investigation task was conducted in home-cage, minimizing exploratory and anxiety behaviors in response to a novel environment. In such conditions, we showed that, compared to WT mice, the sniffing investigation displayed by STOP null mice was lower, while this difference was erased when mice were long term NL treated.

Social investigations and aggressive behavior depend on olfaction integrity since peripheral anosmia results in the failure to induce attack against an intruder and reduced social interactions (Thor and Flannelly, 1977 ; Liebenauer and Slotnick, 1996). The findings of a fairly good olfactory detection of food and of a modulation by NL of the sniffing investigation of social stimuli support the reduced sniffing investigation of a conspecific by STOP null mice was mainly due to a deficit in social interactions. Furthermore, since STOP null mice have been shown to be hyperactive (Andrieux et al., 2002 ; Brun et al., 2005), the decrease in social interaction may not result from a decrease in motor activity. This result strengthens the social interaction deficit previously described in these mice (Andrieux et al., 2002). Such deficit could be related to social withdrawal seen in schizophrenic patients (Andreasen and Olsen, 1982).

STOP null mice exhibited deficits in working memory

One of the more studied and reproducible impairment in schizophrenia is an impairment in working memory (Goldman-Rakic, 1994 ; Kim et al., 2004). Working memory requires the ability to rapidly form memory traces of unique events and the ability to distinguish currently valid information from older and already-invalid information. Extensive description of methods for testing learning and memory processes in rodents focusing on different aspects of memory are described in literature (Castner et al., 2004 ; Powell and Miyakawa, 2006). Spontaneous alternation task in Y-maze has the advantage to measure behavior related to spatial exploration while factors which may influence performance such as motivational or emotional states are minimized. The performance in Y-maze does not involve the learning of a rule because it taps on an innate tendency of rodents to explore new environment and the short-term storage and retrieval of previous trial choices in Y-maze alternation is related to working memory (Wall and Messier, 2002). Notably, in our study, performance of WT mice are relatively low compared to typical alternation rates (about 65%) **(ref ??? Mélina)** . This discrepancy could be explain by the mouse strain used in our study, i.e. mixed BALBc/129 SvPas. In fact, 129Sv mice have been shown to have poorly performance in cognitive tasks (Brooks et al., 2005 ; Contet et al., 2001). This behavioral disturbance is probably due to the dysgenesis of the corpus callosum exhibited by this strain (Duysen and Lockridge, 2006). The largely reduced alternation rates exhibited by STOP null mice suggest impairment in short term spatial working memory. Furthermore, the total number of arm entries similar in both genotypes suggests that basal locomotor activity is not altered in STOP null mice in the Y-maze narrow environment. Reduced alternation rates in STOP null mice are then probably not associated to a decrease of the explanatory behaviors.

Because working memory is a temporary memory system composed of distinct, but overlapping cognitive processes, it is difficult to ascertain the precise nature of the working memory impairment with spontaneous alternation task in Y-maze (Powel and Miyakawa, 2006). Defects in motivation for novelty and/or in attentional mechanisms, that are also among the features of cognitive impairments in schizophrenia, cannot be excluded (Hughes, 2004).

STOP null mice exhibited deficits in learning

Another major aspect of cognitive impairments in schizophrenia is impaired long-term explicit or declarative memory. In rodents, this type of memory has been subject of numerous behavioral studies using tasks based on the olfactory sensory modality. Recognition of individual conspecifics is important for social behavior and requires the formation of memories for individually distinctive social signals mainly mediated by olfactory cues (Carr et al., 1980 ; Kendrick et al., 1997). Conspecific recognition test developed by Hunter and

Murray (1989) allows to study the rodent's recognition memory capacity for odors. In a first odour presentation, the tested animal must take olfactory information, encodes and maintains it throughout a delay in the absence of the olfactory information. In further odor presentations, the animal must determine whether a new odor perception matches (familiarity) or does not match (novelty) the first encountered odor. In familiarity conditions, a decrease in the time duration for current olfactory exploration reveals habituation, while, in novelty conditions, a long time duration for current odor exploration shows discrimination capacity. In this test, WT mice exhibited responses showing habituation and discrimination that imply memory for the first conspecific contact over trials, according to Hunter and Murray's model. On the contrary, STOP null mice exhibited constant and low responses over trials, suggesting that these animals exhibited deficit in learning processes and/or were not interested in this test.

Since STOP null mice defects observed in the conspecific recognition test could be explained in terms of learning and/or motivational process deficits, a spatial learning paradigm associated with an appetitive stimulus was used in order to reinforce motivational processes. According to the visible raisin paradigm of the spatial learning test, the absence of difference between genotypes in the number of mice succeeding in finding food suggest that the time duration available for each trial counteracts a possible deficit in food palatability. In the hidden raisin paradigm of the spatial learning test olfactory guided test, while, over trials, the retrieving capacity of WT mice improved indicating habituation, the STOP null mice's performance remained very low and constant, confirming the difficulties for these mice to learn.

Social and cognitive deficits in STOP null mice are linked to negative symptoms and cognitive impairment in schizophrenia

From a comprehensive behavioral test battery and using multiple overlapping criteria, the present study added to previous ones reveal that STOP gene deletion in mice leads to multiple behavioral abnormalities relevant to schizophrenia including abnormalities relevant to negative symptoms and cognitive impairments. Thus, STOP null mice exhibit altered aggression behavior on resident intruder essay, decreased nesting and nurturing behavior (Andrieux et al, 2002) and decreased home-gage social interaction (this study) indicating of social isolation or withdrawal. Such social dysfunction is considered as similar to the social dysfunction taken into account as a prominent negative sign or symptom in schizophrenic patients (Powell and Miyakawa, 2006). In addition, STOP null mice exhibit decreased sensorimotor gating (PPI deficits, Fradley et al., 2005), decreased performance in a working memory task (this study), and decreased spatial and social learning affecting both habituation and discrimination (this study). Altogether, these abnormalities are indicative of cognitive dysfunction in STOP null mice relevant to the cognitive impairments of schizophrenia. The deficit in learning largely prevent to submit STOP null mice to behavioral tests requiring often complex and sophisticated tasks to be specific to each cognitive process. Moreover, possible poor food palatability and high latency in completing tasks in most of tests might suggest that STOP null mice exhibit a deficit in motivation also largely altered in schizophrenia.

Even if a vast array of different brain regions and neurochemical systems are involved in the modulation of social and cognitive behaviors, the hippocampus and/or the prefrontal cortex and glutamatergic and/or dopaminergic systems are actually involved. In rodents, the prefrontal cortex, has been implicated in a variety of cognitive and executive processes such as the different forms of memory which refer to the capacity to encode, store and retrieve information (for review see Dalley et al., 2004) including the control of the spontaneous alternation (Lalonde, 2002). At the neurochemical level, cognition processes are under the induction and the maintenance of a persistent activity in the prefrontal cortex and related networks via the interactions of dopamine and glutamate N-methyl-D-aspartate receptor signalling (Castner and William, 2007). On an another hand, if glutamate is thought to be essential in memory and learning processes taking place in the hippocampus formation (for review see Morris, 2006), accumbal dopaminergic activity is required in processing social novelty and novel social stimulus discrimination (De Leonibus et al., 2006). It has been also concluded from an extensive review of the literature that cholinergic mechanisms modulate learning and memory processes by altering the balance of the contributions of different neural systems to learning (Gold, 2003). Finally, at the cellular and molecular level, it is well admitted that the neurobiological substrate memories reside in activity-driven modifications of synaptic strength and structural remodeling of neural network activated during learning (for review see Morris, 2006). Accordingly, dysregulation in glutamate and dopamine interactions associated with aberrant activity in, and integration of, the components of distributed circuits involving the prefrontal cortex, the hippocampus and the dopaminergic limbic tract are thought to play an important role in the pathophysiology of the negative symptoms and cognitive impairments of schizophrenia (for review see Gothelf et al., 2000 ; Volk and Lewis, 2002 ; Kuperberg and Heckers, 2000 ; Goff and Coyle, 2001).

Strikingly, STOP null mice exhibit synaptic defects in the hippocampus, including depleted glutamatergic vesicle pool, marked decrease in long-term potentiation and depression in the CA1 field (Andrieux et al., 2002) and in levels of mRNAs encoding synaptic proteins, such as synaptophysin, growth-associated protein-43, and spinophilin (Eastwood et al., 2007). At the neurochemical level, STOP null mice display dopamine hyper-reactivity, preferentially in the limbic dopaminergic system (Brun et al., 2005) and alterations in cholinergic transmission notably in the hippocampus (Bouvrais-Verret et al., 2007). Finally, several indirect evidence support alterations in glutamatergic transmission (Andrieux et al., 2002 ; Bégou et al., 2007 ; Brenner et al., 2007).

Altogether, STOP null mice behavioral deficits are relevant to negative symptoms and cognitive impairment of schizophrenia not only because they are almost identical in humans such as social withdrawal or learning and memory, but also because such behaviors rely on neural and/or neurochemical substrates known to be altered in STOP null mice and implicated in schizophrenia.

Neuroleptic effects

According to our results, we then propose that STOP null mice could be a very relevant animal model to test new treatment to improve social and cognitive defects. Here, as a proof of concept, the effects of a combined treatment with two typical NL, i.e. haloperidol and chlorpromazine, were tested. In STOP null mice, this treatment has already shown to induce beneficial effects notably on hyperlocomotor behaviors (Brun et al., 2005) and glutamatergic vesicular pool in hippocampus (Andrieux et al., 2002).

Here, we show that long term NL treatment can slightly improve social interactions in STOP null mice by restoring the non-aggressive component of the social exploration in the conspecific recognition test. The effects of typical NL on social withdrawal are still in debate in human (Sergi et al., 2007). Many studies on animal models for schizophrenia have however shown beneficial effect of haloperidol on social behaviors tested in a way similar to ours (Steinpreis et al., 1994 ; Black et al., 2002 ; Becker and Grecksch, 2003).

From the present study, the effect of NL treatment is more ambiguous on learning capacities in mice. While NL treatment seems to improve social habituation but not social discrimination in STOP null mice, it seems to have a deleterious effect on both habituation and discrimination in WT mice. In the spatial learning test guided by olfactory cues, NL treatment does not significantly modify the performance of both WT and STOP null mice. Taken together, these results suggest that long term treatment with typical NL does not improve learning capacities of STOP null mice but could have further negative effect on cognitive performance of WT mice. These observations are in agreement with data from literature showing typical NL noxious for learning and memory on healthy people **(REF Melina ou Mohamed/Thierry)** . Even if a more compelling proof of concept would be achieved in testing the effect of atypical NL in STOP null mice, these initial results are really convincing to argue that STOP null mice represent a relevant model to develop drugs targeting cognitive and social symptoms of schizophrenia.

Conclusion

Altogether, in addition to the behavioral changes relevant for positive symptoms of schizophrenia, STOP null mice display some social and cognitive deficits that may be of relevance to schizophrenia. Thus, STOP null mice could be used to investigate novel treatment targeting some of the cognitive disturbances of schizophrenia. In this order, STOP null mice have still been used to evaluate a promising new therapeutic targets for psychiatric disease and more especially schizophrenia, the epothilone D, a microtubule stabilizer (Andrieux et al., 2006).

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Abbreviations

DISC1 : Disrupted In Schizophrenia 1
MAP6 : Microtubule Associated Protein 6
NL : neuroleptics
PPI : Pre-Pulse Inhibition
STOP : Stable Tubule Only Polypeptide
WT : wild-type

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Figure 1

Y-maze spontaneous alternation performance in drug free WT and STOP null mice

The performance of WT and STOP null mice was expressed as the mean alternation ratios ± SEM (a) and the average number of arm entries ± SEM (b) for the overall 8-min session. **p<0.01, unpaired Student's t -test.

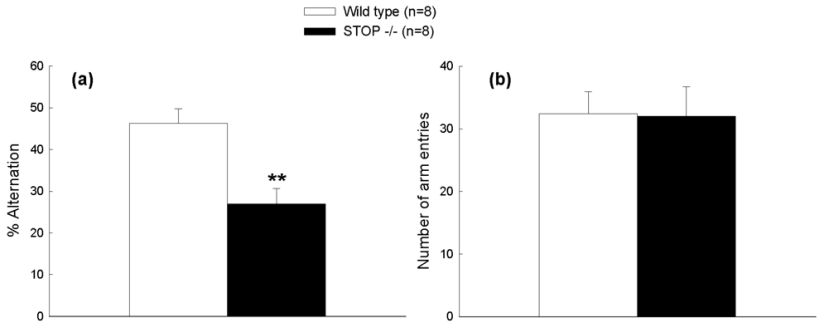


Figure 2

Hidden raisin test in drug free WT and STOP null mice

In each trial, the performance of each genotype was expressed as the percentage of mice succeeding to find a raisin hidden beneath the bedding (a) and the latency to find it (mean±SEM) (b). (a) #p<0.05, compared to corresponding WT mice (chi-square test). (b) **p<0.01, compared to corresponding WT mice (unpaired Student's t -test); $p<0.05 and $$p<0.01 compared to trial 1 (paired Student's t -test).

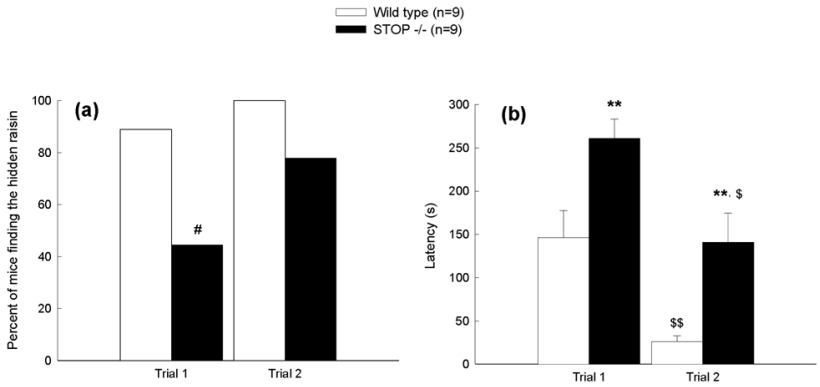


Figure 3

Spatial learning olfactory guided test in drug-free (a, b) and long term NL treated (c, d) WT and STOP null mice

The performance of drug free (a, b) and long term NL treated (c, d) mice was expressed as the percentage of mice succeeding to find a visible or hidden raisin (a, c) and as the latency to find it (mean±SEM) (b, d). On a and c, data depict the percentage of mice able to locate under cut-off a raisin placed either on the surface (T0) or buried beneath bedding in three successive trials (T1 to T3). (# p<0.05 and ## p<0.01 compared to corresponding WT mice, chi-square test). On b and d, data depict changes in latency required by mice to locate food (*p<0.05 and ***p<0.001 compared to corresponding WT mice, unpaired Student's t -test; &p<0.05 T1 compared to T0; $p<0.05, T3 compared to the T1, Newman-Keuls test).

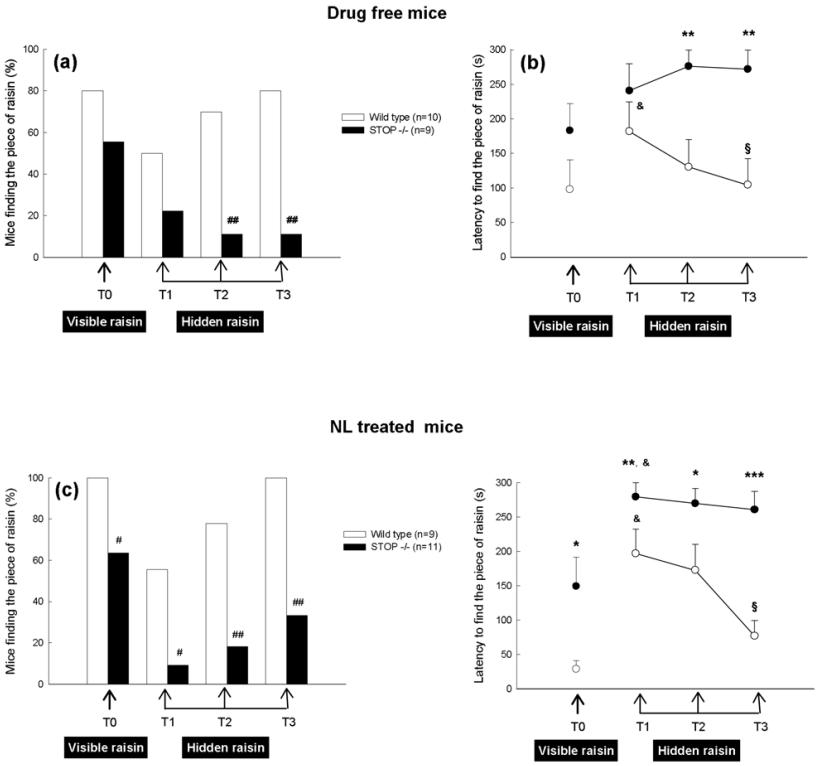
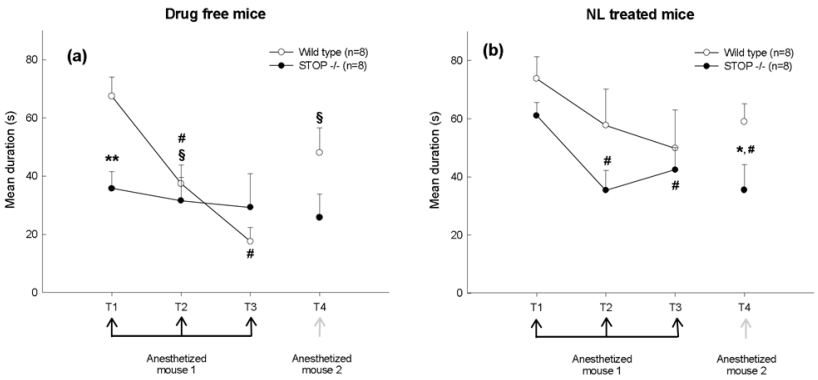


Figure 4

Conspecific recognition test in drug free (a) and long term NL treated (b) WT and STOP null mice

The exploration activity of an anaesthetized intruder mouse by resident mice is presented as the duration of sniffing (mean ± SEM), cumulated for each 3-min trial (T1-T4). In the first three trials (T1 to T3), the same anaesthetized intruder (mouse 1) was used; in the fourth trial (T4), a novel anaesthetized intruder (mouse 2) was introduced in the resident cage. Sharps represent a significant decrease in sniffing duration for each trial compared to T1 (#p<0.05, Newman-Keuls comparisons). Section signs denoted a significant difference in sniffing duration at T2 and T4 compared to T3 (§p<0.05, Newman-Keuls comparisons). Asterisks represent a significant difference between WT and STOP null mice at the same trial (*p<0.05 and **p<0.01, unpaired Student's t -test).