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Short communication

Altered social cognition in male BDNF heterozygous mice and following chronic methamphetamine exposure

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HIGHLIGHTS

- Social cognition was reduced by chronic methamphetamine (METH) in male mice.
- Social cognition was also impaired in male BDNF heterozygous mice.
- Trend for no additive effects of METH and BDNF depletion on social cognition.
- Females showed no changes, and sociability and non-social cognition were normal.
- BDNF may mediate social cognitive changes in schizophrenia and METH psychosis.

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ABSTRACT

Growing clinical evidence suggests that persistent psychosis which occurs in methamphetamine users is closely related to schizophrenia. However, preclinical studies in animal models have focussed on psychosis-related behaviours following methamphetamine, and less work has been done to assess endophenotypes relevant to other deficits observed in schizophrenia. Altered social behaviour is a feature of both the negative symptoms and cognitive deficits in schizophrenia, and significantly impacts patient functioning. We recently found that brain-derived neurotrophic factor (BDNF) heterozygous mice show disrupted sensitization to methamphetamine, supporting other work suggesting an important role of this neurotrophin in the pathophysiology of psychosis and the neuronal response to stimulant drugs. In the current study, we assessed social and cognitive behaviours in methamphetamine-treated BDNF heterozygous mice and wildtype littermate controls. Following chronic methamphetamine exposure male wildtype mice showed a 50% reduction in social novelty preference. Vehicle-treated male BDNF heterozygous mice showed a similar impairment in social novelty preference, with a trend for no further disruption by methamphetamine exposure. Female mice were unaffected in this task, and no groups showed any changes in sociability or short-term spatial memory. These findings suggest that chronic methamphetamine alters behaviour relevant to disruption of social cognition in schizophrenia, supporting other studies which demonstrate a close resemblance between persistent methamphetamine psychosis and schizophrenia. Together these findings suggest that dynamic regulation of BDNF signalling is necessary to mediate the effects of methamphetamine on behaviours relevant to schizophrenia.

Convergent epidemiological, genetic and behavioural evidence suggest that persistent psychosis in methamphetamine (METH) users shows close similarities to schizophrenia, and may in fact represent the onset of schizophrenia in vulnerable METH users [1–5]. Although these similarities extend beyond the psychotic features of both illnesses to aspects of the negative symptoms and cognitive deficits observed in schizophrenia [4,5], preclinical studies in animal models have tended to focus on studying the molecular mechanisms underlying METH psychosis. These studies primarily used sensitization paradigms as this process is thought to closely reflect the signalling changes underlying dopamine system hyperactivity in schizophrenia [6]. Further investigation of cognitive, social and affective behaviours relevant to schizophre-

Abbreviations: HETs, heterozygous mice; BDNF, brain-derived neurotrophic factor; METH, methamphetamine; WT, wildtype.

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Table 1
Number of animals used in each experiment.

	Male				Female			
	WT-saline	WT-METH	HET-saline	HET-METH	WT-saline	WT-METH	HET-saline	HET-METH
Cohort 1	13	13	12	13	14	13	13	12
Cohort 2	11	11	12	12	13	16	12	14
Total	24	24	24	25	27	29	25	26

SAL = Saline pre-treated, METH = METH pre-treated, HET = BDNF heterozygous mice.

nia in METH sensitization animal models may help to evaluate the relevance of METH psychosis to schizophrenia, and also to understand neurobiological changes contributing to these disrupted behaviours across both conditions. Negative symptoms and cognitive deficits in schizophrenia significantly impair patient functioning [7], and improved understanding of their neurobiology will aid the development of new targeted treatments.

Brain-derived neurotrophic factor (BDNF) has been implicated in the pathophysiology of schizophrenia [8,9], and the neuronal response to METH and other stimulant drugs [10]. We recently showed that BDNF heterozygous mice (HETs) do not show a sensitized response to amphetamine following chronic METH exposure during late adolescence [11]. In fact, these mice show an elevated locomotor response to amphetamine and disruption of prepulse inhibition at baseline [11,12], suggesting that they may be 'endogenously sensitized'. In the present study, we aimed to expand the characterization of this model to include behaviours relevant to the negative symptoms and cognitive deficits of schizophrenia.

To this end, male and female BDNF HETs and wildtype (WT) littermates, derived from a breeding colony at the Florey Institute of Neuroscience and Mental Health, were treated with escalating doses of METH (Methamphetamine-HCl, the National Measurement Institute, Sydney, Australia) or saline, from 6 to 9 weeks of age as previously described [11,12]. This colony was originally established with breeders from JAX Mice and Services (Bar Harbour, ME, USA) and maintained on a C57Bl/6 background (>10 generations). All experiments were approved by the institutional Animal Experimentation Ethics Committee. Following at least 2 weeks withdrawal from chronic METH treatment, at 3 months of age, mice were tested for social behaviour in a three-chamber apparatus (clear acrylic) and for short-term spatial memory in a Y maze (wood) as previously described [13,14] under low lighting (50–60 lx in testing arena). Two cohorts of mice were used, the first was tested in the Y maze followed by the three-chamber task, the second was only tested in the three-chamber task. The number of mice used in each cohort is detailed in Table 1.

The three-chamber social interaction task assesses sociability relevant to social withdrawal in the negative symptoms of schizophrenia, and social novelty preference relevant to social cognitive deficits in schizophrenia [13]. First, mice were able to freely explore all three chambers of the empty apparatus for 5 min. They were then directed to the centre chamber, and an empty cup and a cup containing a 'stranger' mouse were placed in the side chambers. The experimental mice were then allowed to freely explore for 10 min. Next, the mouse was directed to the centre chamber and the empty cup was replaced by a cup containing a new 'stranger' mouse. Again, experimental mice were allowed to freely explore for 10 min. Data presented are for exploration during the first 5 min of the second and third phases. Unfamiliar, same sex, SV129/ImJ strain mice that were 2–5 months of age were used as stranger mice. For both phases of the three-chamber task, the second cohort that was tested showed higher exploration of the cups, and greater social/novel cup preference. However, there were no differences in the effects of BDNF genotype or METH treatment on these social preferences between the cohorts, so these data were pooled to increase statistical power for the detection of altered social behaviour between the experimental groups.

The Y-maze task assesses short-term spatial memory relevant to visual cognitive deficits in schizophrenia. Mice were tested in two trials separated by a one-hour inter-trial interval [14]. During the first trial, mice were allowed to freely explore two of the three arms of the Y-shaped maze for 10 min. During the second phase, mice were able to freely explore all three arms for 5 min, with the previously inaccessible arm designated the 'novel' arm.

Videos from both tasks were analysed using CleverSys Topscan software (Clever Sys Inc., Reston, USA) to track animal exploration in the testing chamber and to measure interaction time in the three-chamber task. Here, a 10 mm "extended radius" was traced around the cups, and this zone was used to detect object sniffing or interaction. Statistical analysis was conducted using SYSTAT 9 software, and three-way repeated measures ANOVA statistics were used to test the effects of sex, METH treatment and genotype on preference in the tasks. To assess preference in three-chamber task and Y-maze, empty and social cups and chambers, novel and familiar cups and chambers, and novel and other arms were included as variables for repeated-measures analyses. All graphs show mean + SEM.

During the first phase of the three-chamber task, all groups showed a strong preference to interact with the stranger mouse compared to the empty cup, and there were no differences between the experimental groups in this preference, suggesting that sociability was normal in both male and female BDNF HETs and following METH treatment (Fig. 1A, B; main effect of cup, $F_{(1,196)} = 309.7$, $p < 0.001$, no further interactions). This was supported by preferential exploration of the social zone in the 3-chamber apparatus (Fig. 2A, B; main effect of chamber, $F_{(1,196)} = 138.4$, $p < 0.001$). During the second phase of the three-chamber task, the time spent interacting with a novel stranger and the now familiar first mouse was used to assess social novelty preference. Unlike sociability, there were sex-dependent effects of genotype and METH treatment on social novelty preference (Fig. 1C, D; cup × sex × genotype interaction, $F_{(1,198)} = 4.1$, $p = 0.043$; cup × sex × METH treatment interaction, $F_{(1,198)} = 3.9$, $p = 0.049$). The sexes were separated and further ANOVAs performed to interrogate this interaction. In males, social novelty preference was reduced to ~50% of control levels following METH treatment, and by more than one third in BDNF HETs relative to WT saline-treated controls (Fig. 1C, males only: cup × METH treatment interaction, $F_{(1,95)} = 11.4$, $p = 0.001$; cup × genotype interaction, $F_{(1,95)} = 5.0$, $p = 0.027$). In addition, there was also a trend for METH treatment × genotype interaction, reflecting that while male BDNF HETs that are treated with saline showed reduced social novelty preference compared to WT controls, there was no further reduction in BDNF HETs treated with METH compared to their METH-treated WT controls (males only, cup × genotype × METH treatment interaction, $p = 0.075$). In contrast to males, there were no significant effects of genotype and METH treatment on social novelty preference in females (Fig. 1D). Exploration of the three-chamber apparatus supported these findings, with significant effects of sex, genotype and