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Aberrant acoustic and tactile sensory processing at specific developmental stages in the *Cntnap2* and *Nrxn1* mouse models for neurodevelopmental disorders

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tal enrichment on the behavioral and structural alterations in rats prenatally exposed to valproic acid (VPA).

Methods: Female outbred white rats were mated overnight, and the morning when spermatozoa were found was designated as the first day of gestation. Females received a single intraperitoneal injection of 500 mg/kg sodium VPA on the 12.5 day after conception, and control females were injected with physiological saline at the same time. On the postnatal day 7 (PND7) half of the offspring from Control (C) and VPA treated (V) group were housed in an enriched environment (EE) and the other half were reared in standard environment (SE). Behavioural experiments started on postnatal day (PND) 30 - 35. Sociability was evaluated in a three-chamber apparatus, Eye opening was observed from days 12 to 16. Purkinje cell loss in cerebellum was evaluated by the classical histological Nissl staining method.

Results: Our results showed maturational delay - later eye opening in prenatally VPA treated groups. In the sociability test V-SE group stayed more time in the empty space and their staying time in the compartment with a conspecific rat was significantly lower than in V-EE groups ($P = 0.013$) suggesting the deficits in sociability, but was lower than in the control group ($P < 0.01$). Our results showed that the total number of Purkinje cells in the V-EE group was significantly higher than in the V-SE group but was lower than in the C-SE and C-EE groups.

Conclusions: In conclusion, the present study demonstrates that the environmental enrichment during early developmental age improves deficit in sociability in a VPA-exposed rat model of ASD and it prevents prenatal VPA-induced loss of Purkinje cells in the cerebellum. Our results bring further support to the validity of the proposed VPA animal model of autism and reinforce the importance of this model for the preclinical investigation of new therapeutic approaches.

Conflict of interest

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P.0042

Age related behavioral alterations in rat model of autism

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Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder characterized by early-onset impairments in social communication and social interaction repetitive behaviors, stereotypies, and a limited repertoire of interests and activities. The first cohort of identified children are only now entering old age. Despite progress in understanding of autism, relatively little attention has been paid to date to the process of aging. A limited number of human studies have investigated the persistence of the ASD core deficits into adulthood. As aged human studies are limited animal models can be used to study the behavioral alter-

ations at different age in more detail and in a more controlled environment.

The valproic acid (VPA) rat model is an environmentally triggered model with strong construct and clinical validity. The rats exposed to a single dose of VPA on embryonic day 12.5, around the time of neural tube closure, present neuroanatomical and behavioral characteristics similar to human autism. While the autistic-like behavioral phenotype of the young VPA rat model has been studied extensively, the effects of age on this ASD-like rat model have not been elucidated.

Females received a single intraperitoneal injection of 500 mg/kg sodium VPA on the 12.5 day after conception, and control females were injected with physiological saline at the same time. Autism-related anxiety-related behavior and social behavior, spatial memory and development of learning process were studied in control (group - C) and prenatally VPA (group - V) treated rats at two different ages: postnatal day 30 (P30) and middle aged (M - 6 months) rats.

In Morris water maze testing all rats exhibited a decreased latency to find the hidden platform across the eight training trials. During the probe test which was performed 1 hour or 3 days later after task acquisition trained rats of all groups spent significantly longer than chance in the test quadrant where the hidden platform was located in training trials and did not differ significantly among each other. Our study showed marked decreases in social interaction in VPA-treated rats. In the sociability test, VPA rat stayed more time in the empty space than rat in control group and their staying time in the compartment with a conspecific rat was significantly lower than control rat suggesting the deficits in sociability. We also evaluated the social behavior by measuring approaching time (sniffing time) to either wire cage with rat or empty wire cage. The M/VPA rat showed a significantly lower social approach than the control rats of both age groups or the P30/VPA rat. Measures of anxiety, the time spent in the open arms and the number of open arms entries, differed significantly between M/VPA and P30/VPA rats; M/VPA rats were more anxious compared to all other groups of animals. The identification of short-term and long-term behavioral characteristics in prenatally VPA treated young and adult rats enhance our understanding of autism and to gain further insight into the effects of aging in ASD.

Conflict of interest

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P.0043

Aberrant acoustic and tactile sensory processing at specific developmental stages in the *cntnap2* and *nrxn1* mouse models for neurodevelopmental disorders

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Sensory information processing is key for normal functioning in daily life. Sensory abnormalities are a frequent feature of neurodevelopmental disorders (NDD). In autism spectrum disorders (ASD) sensory abnormalities are reported in up to 90% of patients. Moreover, these symptoms are reported as early as 6 months of age while diagnosis generally takes place at 3 years of age or later. This suggests that deficits in sensory processing could possibly underlie other symptoms found in NDD. However, it is unclear which biological mechanisms underlie these sensory symptoms and when during development these changes could contribute to a behavioural phenotype. Therefore, the aim of this research was to perform a longitudinal screening of the behavioural sensory phenotype in genetic mouse models of NDD.

To this end, we assessed acoustic and peripheral tactile sensory sensitivity by measuring startle responses to single auditory and tactile stimuli. In addition, prepulse inhibition (PPI) of paired auditory and auditory-tactile stimuli was measured to assess sensory gating. These tests were performed in two genetic models associated with NDD: *Nrxn1*^{-/-} and *Cntnap2*^{-/-} mutant mice with their respective WT littermates serving as controls. This multi-model approach was used with the aim of finding convergence in possible underlying biological mechanisms of NDD. In addition, sensory phenotypes were monitored at three different developmental timepoints (TP1 6-8 weeks, TP2 12-14 weeks and TP3 18-20 weeks) with the goal of identifying possible sensitive time windows. Significance was ascertained by repeated measures ANOVA with corrections for multiple comparisons.

A significant main effect of genotype and a genotype x sound level interaction was found for acoustic sensory sensitivity in both the *Nrxn1* and *Cntnap2* mice (*Nrxn1*: $p=0.0013$; *Cntnap2* $p=0.0371$, interaction: *Nrxn1*: $p=0.0095$ *Cntnap2* $p=0.0013$). Both gene knockout models showed a decrease in acoustic sensitivity for higher dB acoustic pulses (110-120dB). In addition, the *Cntnap2*^{-/-} mice showed decreased peripheral tactile sensitivity. Moreover, for the acoustic and tactile-acoustic sensory gating a main effect of both age and genotype was found for both mouse models (Age $p<0.001$, acoustic *Cntnap2*: $p<0.001$; *Nrxn1* $p=0.0133$, tactile-acoustic *Cntnap2* $p=0.0018$; *Nrxn1* n.d.). *Nrxn1*^{-/-} and *Cntnap2*^{-/-} mice showed increased levels of PPI indicating aberrant sensory gating. Interestingly, the decreased acoustic sensitivity and increased sensory gating effects were not yet visible during the first timepoint at 6-8 weeks. Conversely, peripheral tactile hyposensitivity in the *Cntnap2* was most prominent at the earliest timepoint at 6-8 weeks.

Here, we show that tactile and acoustic sensory sensitivity and gating is affected in two mouse models for NDD, specifically at later developmental stages (early and late adulthood), but not yet during early adolescence. Interestingly, the peripheral tactile phenotype was specifically clear at the first time point, while the central acoustic sensory phenotypes were most apparent at later stages. To further determine the origin of the behavioural deficits observed in these mice, our next step is to identify changes in brain markers related to sensory processing during these time points. Ultimately to further unravel underlying biological mechanism as well as identifying optimal developmental time windows for new therapeutic strategies for NDD.

Conflict of interest

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P.0044

Memantine improves social behavior in rats exposed prenatally to valproic acid

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Background: The term "autism spectrum disorders" (ASD), is used to describe a group of neurodevelopmental disorders which are characterized by impairments in communication and social interaction, repetitive behaviors and a limited repertoire of interests and activities. The etiology of autism is not known, but it has strong genetic and environmental components. Rats prenatally exposed to valproic acid (VPA) showed autistic behaviors; decreased sociability, increased repetitive behavior, hyperactivity. Although the number of patients has strikingly increased in the last ten years, therapeutic agents to ameliorate the ASD core symptoms are very limited. In this study, we investigated therapeutic potential of memantine for ASD using VPA-induced autistic animal model. Memantine is uncompetitive antagonist of glutamatergic NMDA receptors. In addition, memantine has been demonstrated to act as an antagonist of nicotinic acetylcholine receptors. Hyperactivity of the excitatory glutamate system and dysregulation of acetylcholine (ACh) has been theorized to have a causal role in the development of behavioral symptoms in autism.

Methods. Female outbred white rats were mated overnight, and the morning when spermatozoa were found was designated as the first day of gestation. Females received a single intraperitoneal injection of 500 mg/kg sodium VPA on the 12.5 day after conception, and control females were injected with physiological saline at the same time. Control and VPA rats were divided into 2 subgroups and memantine (5 mg/kg of body weight) or saline was administered via intraperitoneal injection from postnatal day 14 to 35, once daily. The rat is allowed to explore a novel object (wire cage) and a stranger rat, inside a wire cage placed separately at both ends of the chamber. The time spent in each chamber and time sniffing the wire cage or the caged animal is measured.

Results. Results showed marked decreases in social interaction of VPA-treated rats. In the sociability test, VPA rat stayed more time in the empty space than rat in other groups and their staying time in the compartment with a conspecific rat was significantly lower than control rat suggesting the deficits in sociability. Interestingly, VPA group treated with memantine stayed more time in the compartment with a conspecific rat which showed improved social interaction by the memantine. We also evaluated the social behavior by measuring approaching time (sniffing time) to either wire cage with rat or empty wire cage. VPA rat showed significantly lower social approach. Meman-