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Short communication

Inequity aversion is observed in common marmosets but not in marmoset models of autism induced by prenatal exposure to valproic acid

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ABSTRACT

Humans and various nonhuman primates respond negatively to inequity not in their favor (i.e., inequity aversion), when inequity between two individuals is introduced. Common marmosets, a highly prosocial species, further discriminated between human actors who reciprocated in social exchanges, and those who did not. Conversely, marmoset models of autism, induced via prenatal exposure to valproic acid (VPA marmosets), did not discriminate. Interestingly, previous studies of inequity aversion in marmosets have produced negative results, or were limited to males. Recent studies suggest that inequity aversion is highly influenced by the tasks employed. Here we show inequity aversion in both male and female marmosets using a novel task which required a relatively long duration of response. Marmosets were required to hold a spoon for 2 s to receive a reward. Marmosets successfully performed the task when they observed an unfamiliar conspecific partner obtaining the same reward (equity test). However, when they witnessed the partner receiving a more attractive reward for equal effort (inequity test), unexposed marmosets, which were not exposed to either valproic acid or saline during the fetal period refused to respond. This inequity aversion was not observed in unexposed marmosets when the partner was absent. In contrast, marmosets with fetal exposure to valproic acid (VPA marmosets) successfully executed the task irrespective of their partners' reward conditions. As prenatal exposure to valproic acid is a well-known procedure to induce autism spectrum disorder (ASD)-like behaviors in rodents, we propose that VPA marmosets failed to show inequity aversion due to weak social motivation or interest towards others.

Humans and common marmosets share critical features in their social relationships. Both live with family members (and other non-family members in the case of humans). Polygamous and polyandrous constellations occur [1] in both species. Neverthelss, individuals other than the genetic parents help to care and provide for offspring (i.e. both utilize a cooperative breeding system) [2]. Humans and common marmosets are highly prosocial [3]. Marmosets show human-like hypersociality [4], such as concern for others, proactive food-sharing [5], targeted helping [6], and cooperation with non-relatives and near-strangers [7]. These similarities in the social relationships, behavioral abilities, and social cognition of humans and marmosets have led common marmosets to be regarded as an ideal primate species to study biological and evolutionary foundations of human social cognition [8–11], especially in the field of autism spectrum disorder (ASD) research, owing to the high socio-cognitive skills of marmosets [12]

In a preceding study, we demonstrated that a primate model for ASD failed to recognize third-party reciprocal exchanges and their violation [13], while unexposed marmosets, which were not exposed to either valproic acid or saline during the fetal period did discriminate between a third-party's reciprocal and non-reciprocal exchange [12]. In these studies [12,13], we enlisted actors to perform short plays for untreated marmosets. In one play, a pair of actors exchanged pieces of steamed buns and potatoes. In a second play, one actor took food from his or her partner, but gave nothing in return. After each play, both actors offered a piece of sponge cake to the marmosets. Unexposed marmosets accepted food readily from both actors in the sharing scenario. However, when one actor hoarded the food, the monkeys chose to accept food primarily from that actor's partner. This suggests that marmosets recognize reciprocity and avoid the non-reciprocating actor.

In the following study [12], we gave this social intuition test to

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marmosets exposed in the womb to valproic acid (VPA). Prenatal exposure to this epilepsy drug is known to increase the risk of autism in humans and is widely used to produce rodent models of autism [14,15]. We have already shown that marmosets with prenatal exposure to VPA (VPA marmosets) demonstrate all three core symptoms of autism; namely: 1) biased usage of vocal repertoires, 2) weak social attention to unfamiliar conspecifics, and 3) deficits in reversal learning (Sasaki et al., in preparation). Four unexposed controls (one male and three females), who did not participate in the previous study, accepted food readily from both actors in the sharing scenario, but avoided accepting food from non-reciprocating actors, as consistent with the previous study. In contrast, VPA marmosets did not discriminate between actors in the hoarding scenario; they were just as likely to accept food from the non-reciprocating actor as from the generous one. These findings suggest that marmosets can discriminate between equivalent and inequivalent reward distributions by third-parties, while the VPA-exposed marmosets lack either the social motivation toward others, or the ability to discriminate between reciprocal and non-reciprocal exchange.

Though many primate species show inequity aversion [16,17], marmosets, surprisingly, have failed to show inequity aversion. Inequity aversion refers to the preference for fairness, and resistance to incidental inequalities [16]. If inequity between two individuals is introduced, animals respond negatively to inequity that is not in their favor. Recently, inequity aversion was demonstrated by marmosets (*Callithrix penicillata* and *Callithrix jacchus*), with some limitations [17,18]. Male and female marmosets were tested in a tray-pulling task to determine whether they would donate superior rewards to their long-term pair-mate or to an opposite-sex stranger [18]. Results revealed that male marmosets showed inequity aversion towards their pair-mates, but not towards strangers, while female marmosets did not show any inequity aversion. These sex differences were explained by the differential breeding strategies of males and females; marmoset fathers have higher motivation for parenting than do mothers [19], and male helpers tend to carry more of the child-rearing burden than do female helpers [20]. The number of male, but not female, helpers in a group is typically associated with infant growth rates and survival in the wild [21]. Thus, if inequity aversion serves to maintain cooperative relationships in marmosets, males would be expected to show more inequity aversion than females, owing to the males' greater propensity to maintain cooperative relationships.

Although male marmosets may be expected to show greater inequity aversion than females, there is no reason to deny the existence of inequity aversion in female marmosets. To our knowledge, female marmosets have not been shown to demonstrate inequity aversion at all [17,18]. It is, however, widely accepted that responses to inequity vary according to the task s employed in the study [22,23].

The purpose of this study is double-fold. First, we evaluate whether marmosets, including females, show inequity aversion in a novel task. Second, we examine whether marmosets, exposed to VPA (VPA marmosets) show inequity aversion. Based on our previous study, we predicted that VPA marmosets would not respond negatively to inequity, even if unexposed marmosets (UE marmosets) did show inequity aversion in the novel task. The task employed in this study required the holding of a plastic teaspoon for 2 s. Compared to the standard token-exchange task commonly used in inequity aversion studies, this task may be regarded as relatively high-cost, as marmosets must hold the spoon for a long period of time. We expected that the delayed reward in this task would cause marmosets to be less inclined to execute the response compared to a standard token-exchange task, such that untreated marmosets would show inequity aversion.

Six UE marmosets (two male and four female) and five VPA marmosets (two male and three female), ranging from 3.4 to 5.5 years of age, were used in this study. All marmosets were housed in the same animal room and were born in the National Institute of Neuroscience (NIN). They were cared for by their parents in a pair cage until they reached the weaning period (3 months old), at which point they were moved to live in another pair cage with their littermate until the age of ~1.5 years old. The housing conditions of the unexposed and VPA marmosets were identical. They had free access to water and were fed monkey pellets twice a day. They were also fed supplementary vegetables and fruits. All experimental and animal care procedures were performed in accordance with the Guide for Care and Use of Laboratory Primates published by NIN, National Center of Neurology and Psychiatry and approved by the Animal Research Committee at NIN in Tokyo, Japan.

VPA marmosets were generated as described in a previous study [12]. Three dams of VPA marmosets were mated in their pair cages. Their blood progesterone levels were monitored periodically to determine timing of the pregnancy, as were the UE dams. They received oral injections of 200 mg/kg sodium valproate seven times, from day 60 to 66 after conception. This period was determined with reference to the administration period (E12 of the rat fetus) used to produce a VPA rodent model of autism. All three VPA dams took the medicine without vomiting and did not show any signs of abnormal pregnancy or delivery. Oral injection may have negative impact on pregnant monkey, however, there was no method other than oral injection. Two UE marmoset dams were given neither VPA nor the solvent by oral injection during this period to prevent any risk of miscarriage. The VPA marmosets did not display any malformations or any body weight differences compared to the UE marmosets.

Two identical carrying cages (25 cm × 25 cm × 18.5 cm) served as the test apparatus. The front panel of the cage was a mesh-wire surface. These cages were placed on a table, slightly facing each other (the angle between them was 100 degrees) so that the marmosets could see each other (Fig. 1). A food cup was placed between the cages (28 cm apart). No reward was shown before completion of the spoon-holding in order to encourage the marmosets. A video camera recorded their behavior from 38 cm away from the cages, and an experimenter stood 53 cm away from the cages.

There were two types of reward: the standard reward (a piece of puffed rice) and the high-value reward (a piece of steamed bread), which were chosen by a preference test in the marmosets' home-cages. In the preference test, two types of rewards were presented simultaneously in the hands of the experimenter 40 times in four sessions, and the marmoset could take one of the two rewards in each trial.

The task was a modified version of the spoon-holding training task for marmosets [24]. All marmosets in this study (including partners) were trained to hold a plastic spoon for more than 2 s, initially in their home cage, then in the carrying cage prior to the test. Trials were initiated by presentation of the spoon near the front panel. Marmosets

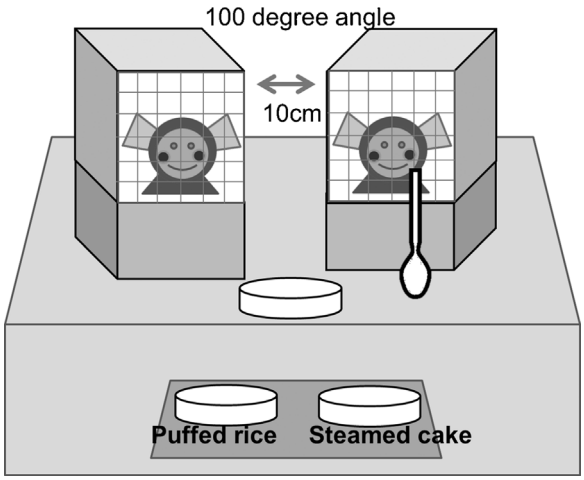

Fig. 1. An illustration of the apparatus and testing set-up for the target and partner marmosets. The pictured trial depicts an inequity test condition. The partner (left) was rewarded with a high-value food, and the target marmoset is watching closely.