

An animal model of autism: behavioural studies in the GS guinea-pig

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Abstract

Autism is a human behavioural pathology marked by major difficulties in abnormal socialization, language comprehension and stereotypic motor patterns. These behavioural abnormalities have been associated with corticocerebral and cerebellar abnormalities in autistic patients, particularly in vermal folia VI and VII. Progress in understanding this disease has been hindered by the absence of a non-primate animal model. GS guinea-pigs are a partially inbred, non-ataxic guinea-pig strain with cerebellar and corticocerebral abnormalities similar to those reported to exist in human patients with autism. In order to determine if GS guinea-pigs represent an animal model of autism, their behaviour was compared with that of Hartley strain guinea-pigs. GS animals learned a motor task significantly more rapidly than Hartley guinea-pigs, but performed it in a more stereotypic manner and were less influenced by environmental stimuli than Hartleys. GS animals exhibited significantly less exploratory behaviour in a novel environment and were significantly less responsive to 50–95 dBA pure tones than Hartley guinea-pigs. In a social interaction assay, GS guinea-pigs interacted significantly less frequently with each other or with Hartley guinea-pigs than Hartleys did under the same conditions. GS behaviour thus exhibits autistic-like behaviour patterns: motor stereotypy, lack of exploration and response to environment and poor social interaction. Coupled with the neuropathological findings, this abnormal behaviour suggests that GS guinea-pigs could be a useful animal model of autism.

Introduction

Autism is a pervasive developmental disorder whose diagnosis is made on the basis of functional abnormalities: impaired social interactions, impaired communication and stereotyped behaviour patterns (Kanner, 1943; Damasio & Maurer, 1978; Curcio, 1978; Mundy *et al.*, 1986, 1990; Dawson & Lewy, 1989; American Psychiatric Association, 1994; Happe & Frith, 1996); it can be associated with other pathologies including mental retardation (De Moura-Serra, 1990). Additional dysfunctions frequently encountered in autism are loss of previously learned motor schemes, reduction in exploration (De Moura-Serra, 1990), selective recognition of auditory stimuli (Bruneau *et al.*, 1987; Lelord & Sauvage, 1991; Lincoln *et al.*, 1992; Bruneau, 1994), disorders of mental development and mental representation of action (Lösche, 1990; Lotspeich & Ciaranello, 1993), and cognitive deficits in the ability to maintain cross-modal associations (Martineau *et al.*, 1992).

Autism has been considered a purely psychological disorder, but, recently, neurophysiological and neuropathological dysfunctions have been demonstrated in autistic children. The mesolimbic cortex,

neotriatum, thalamus (Damasio & Maurer, 1978), amygdala (Fotheringham, 1991), and even the brain stem (Ornitz *et al.*, 1985) have been suggested to be concerned with autism (reviewed in Bauman, 1997). The most impressive studies in the neuropathology and neurophysiology of autism have related to cerebellar abnormalities (Williams *et al.*, 1980; Bauman & Kemper, 1985; Ritvo *et al.*, 1986; Courchesne *et al.*, 1987, 1988, 1994b; Sears *et al.*, 1994). If the role of the cerebellum in the regulation of movement has been known for long, its implication in cognitive and emotional processes has been recognized more recently (Pellionizz & Llinas, 1982; Hamilton *et al.*, 1983; Botez *et al.*, 1985; Courchesne, 1987, 1989, 1991, 1997; Leiner *et al.*, 1989; Ivry & Keele, 1989; Lalonde & Botez, 1990; Lalonde, 1994) despite suggestions for such a role one century ago (reviewed in Schmahmann, 1997).

Autism has been claimed to occur only in human beings (Vidal, 1993), although Bachevalier's studies (1991, 1994) in the rhesus monkey may provide an animal model of autism. However, an experimental analysis of autism on a large scale has been hampered

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by the lack of a non-primate animal model. Recently, a strain of partially inbred, non-ataxic guinea-pigs with cerebellar and cerebrocortical abnormalities has been reported (Lev-Ram *et al.*, 1993). The cerebellar abnormalities (malformation of vermal folia VI and VII) resembled those reported to occur in human patients with autism (Courchesne *et al.*, 1987, 1988). We therefore selected four behavioural patterns corresponding to those frequently observed in autistic infants for examination under laboratory conditions: (i) a motor learning task, as autistic patients may exhibit retardation and stereotypic motor patterns; (ii) spatial exploration, as exploration is reduced in autistic patients; (iii) responses to sounds, as autistic patients are often highly selective in reacting to auditory stimuli; and (iv) social interactions, as these are often disrupted in autistic patients. The responses of the GS guinea-pigs were compared with those of Hartley guinea-pigs. The latter were used as controls for three reasons: (i) they were used as controls in the above-mentioned study of Lev-Ram *et al.* (1993) who showed that their brain presented no sign of abnormality; (ii) they are commonly commercialized (Iffa Credo, France and Charles River France) as 'normal' animals from a behavioural point of view; and (iii) their motor behaviour was similar to that of pigmented guinea-pigs as we have shown in preliminary studies. We have found that GS guinea-pigs respond abnormally in each of these areas, and suggest that they may indeed represent a suitable animal model for autism.

Materials and methods

Animals

GS guinea-pigs are a partially inbred, non-ataxic, long-haired albino strain developed and bred by us (Lev-Ram *et al.*, 1993). Hartley guinea-pigs were obtained from IFFA CREDO (France). Animals were housed in 90 × 40 cm cages as breeding pairs (one male, one female), fed pellets, carrots, apples, maize and hay and supplied with water *ad libitum*. A total of five GS and seven Hartley guinea-pigs were studied. They were 6–8 months old at the beginning of the experiments.

Experimental devices and protocols

All animals were successively submitted to a motor learning task, an exploration task, auditory stimulation and a social interaction procedure.

Motor learning

Motor learning was measured using a rotorod, a horizontal wooden cylinder rotated around its longitudinal axis by a DC electric motor. The rotorod was 15 cm in diameter, 50 cm long, with two large disks 60 cm in diameter at each end, and was covered with foam rubber surfaced with a layer of rough cloth. It was positioned 90 cm above a landing platform covered with a thick carpet to cushion the animal's fall. Each guinea-pig was given a series of 10 trials twice daily (morning and evening). For each trial, the animal was placed upon the rotorod with its body axis perpendicular to the axis of rotation and its head facing against the direction of the rotation so that it had to walk forward to maintain its balance. Each animal was trained at 3 r.p.m. until it could maintain its balance on the rotorod for 3 min at each of the 10 trials of a series (learning criterion), or if it could not, until its scores reached a plateau for 5 successive days. Fourteen days later, the same animals were placed on the rod rotated at 6 r.p.m. until their scores reached the learning criterion or a plateau. A further 14 days later, animals were placed on the rod rotated at 9 r.p.m. until their scores reached the learning criterion or a plateau. Between two

TABLE 1. Number of series of 10 trials needed to reach the learning criterion in Hartley and GS guinea-pigs for the different rotation rates used (3, 6 and 9 r.p.m.). The sign ∞ means that the animal did not reach the learning criterion (their score reached a low-level plateau for 5 consecutive days); the sign ? means that the animals have not been tested, usually because they did not learn the task for a rotation rate just lower

Hartley				GS			
guinea pig no.	3 r.p.m.	6 r.p.m.	9 r.p.m.	guinea pig no.	3 r.p.m.	6 r.p.m.	9 r.p.m.
1	4	5	6	1	5	2	4
2	4	2	∞	2	4	2	3
3	3	12	∞	3	3	4	4
4	8	∞	?	4	4	3	1
5	5	∞	?	5	4	8	∞
6	13	∞	?				
7	∞	?	?				

consecutive trials, a 5 min (3 or 6 r.p.m.) or a 10 min (9 r.p.m.) rest period was allowed. The time during which animals maintained their balance on the rotorod without falling down and the strategy used to keep balance (grasping or walking) was noted for each trial. Results are reported as mean series (\pm SEM) to reach the learning criterion. As the number of series to reach the criterion was different from one animal to the other (see Table 1), the number of tests sessions was different for the different animals of a same group.

Exploratory behaviour

Exploratory behaviour was examined in a 60 × 60 × 40 cm box containing a platform 10 cm above the bottom; 18 holes (8 cm in diameter) had been drilled in this platform. It was divided by a fictitious line into peripheral and central zones of equivalent area including 10 and eight holes, respectively. The box was placed in a fixed position in the experimental room to ensure constancy of brightness and visual cues between experiments. Given that the exploration behaviour of an animal is altered by stress, each animal was placed in the experimental box from which the pierced platform was removed, for 30 min each day for the 2 days preceding the experiments, for the purpose of familiarization and in order to reduce the stress due to the novel environment. Exploratory activity was determined by placing animals in the box containing the platform at the same arbitrarily selected starting point in the peripheral area and allowing them to explore the box for 20 min. Exploration was filmed. The time spent in the peripheral and central areas of the platform, the total number of holes explored (a hole was considered as explored when the animal poked its head down into it), and the duration of motion and motionless periods was noted for each animal. Results are reported as mean holes explored (\pm SEM) and mean time spent in exploration (\pm SEM) as a percentage of total time.

The day after this experiment, the animals were submitted to an extra-testing procedure placing them, one by one, for 4 consecutive days, on the floor of the experimental room, which represented a vast 'open field', and their motor activity was observed for at least 15 min.

Response to auditory stimuli

For measurement of response to auditory stimuli, each guinea-pig was placed in a cage, similar to its familiar cage, located in a soundproof room. In the cage, some pieces of their favourite food were placed because we wanted to know the reaction of the animals to the sound when they were engaged in eating a pleasant food. The animals were exposed to pure tones delivered by a generator connected

to a loudspeaker or to familiar noises. Pure tones were 500, 1000 and 5000 Hz sinusoidal waves at 50, 65, 80 and 95 dBA. Familiar noises were keys clicking, crumpling of a plastic bag (usually containing carrots used to feed the animals), experimenter's voice and squeaks of other guinea-pigs. The animals were placed into the cages for 8.5 min daily for 3 consecutive days (days 1–3) to familiarize them with the novel environment. The sounds were delivered to the animals every 2 days. Fifty dBA 500 Hz, 1000 Hz and 5000 Hz pure tones were delivered on days 4, 6 and 8. Sixty-five dBA pure tones were delivered on days 11, 13 and 15. Eighty dBA pure tones were delivered on days 18, 20 and 22. Ninety-five dBA pure tones were delivered on days 25, 27 and 29. Animals were exposed to the above-mentioned familiar noises on days 32, 34, 36 and 38. Pure tones and familiar noises were delivered for 30 s (three sounds delivered in a randomized fashion), 5 min after the animal was in its cage. It was then allowed to remain there a further 3 min after the noise had stopped. Animal behaviour was filmed during the entire 8.5 min of the experiment, and was noted at the onset of the noise and during the whole auditory stimulation. It consisted in orientation reaction, jumps, escape behaviour, squeaks or sudden immobility (when the animals were eating, for example). The occurrence of a reaction or non-reaction was noted for each pure tone frequency and intensity and for each familiar noise to which GS and Hartley animals were exposed. Results are reported as mean non-response to auditory stimuli (\pm SEM) expressed as percentage of total exposures to stimuli.

Social interactions

Social interactions were measured in cages similar to those used for maintenance. An animal was placed in a test cage for 15 min daily on 3 consecutive days in order to reduce the stress due to the novel environment. The experimental cage was always placed in the same room at the same position at constant brightness, as it has been shown that environment and brightness influence social interactions under these conditions (File & Hyde, 1978). On days 4 and 5, an animal of the same group (GS with GS, Hartley with Hartley) was introduced into the cage. On day 4, a familiar animal was introduced (animal from the same cage), on day 5, an unfamiliar animal from another cage was introduced. On day 6, an animal of the other group was introduced (GS with Hartley, Hartley with GS). The interaction was filmed for 15 min between 6 p.m. and 9 p.m. Active interactions (sniffing, licking, mating attempts), passive interactions (the animal passively receiving contacts from the other animal) and avoidance behaviour were noted from the film. An occurrence of avoidance was deemed to have occurred when the animal receiving contact ran or turned away. Results are reported as mean interaction time (\pm SEM) as a percentage of the total time together, mean active interaction time (\pm SEM) as a percentage of the total interaction time and mean number of occurrences of avoidance (\pm SEM).

Statistical analysis

Data were statistically analysed by the Mann–Whitney test (rotorod), U and t -tests (exploratory behaviour), t -test (reaction to auditory stimuli) and ANOVA (social interactions) using repeated measures for the behavioural activities as there were several data collected on the same animals during the diverse social interactions.

Results

Motor learning

All GS guinea-pigs learnt the task at 3 and 6 r.p.m. and needed 4 ± 0.3 and 3.8 ± 1.1 series of 10 trials, respectively; one of the five

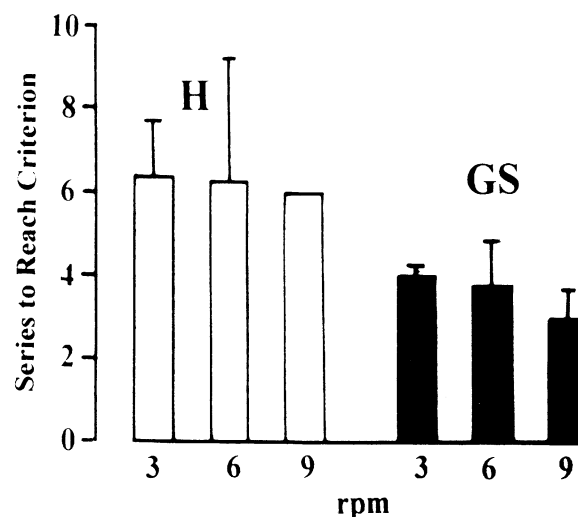


FIG. 1. Motor learning abilities of Hartley and GS guinea-pigs on rotorod are similar. Number of series of 10 trials (mean \pm SEM) required by Hartley (H: open bars) and GS (filled bars) animals to reach learning criterion when rotated at 3, 6 and 9 r.p.m. The difference in number of series required to achieve learning criterion between Hartley and GS is not significant ($P > 0.05$).

failed at 9 r.p.m. and the four learners needed 3.0 ± 0.7 series of 10 trials (Table 1 and Fig. 1). Of the seven Hartley guinea-pigs studied, six reached the learning criterion at 6.2 ± 1.5 series of trials when rotated at 3 r.p.m. These six animals were rotated at 6 r.p.m. 14 days later. Only three reached the learning criterion, needing 6.3 ± 3.0 series of trials. The other three did not reach the learning criterion even after 16 series of trials. Only one animal of the three reaching the learning criterion at 6 r.p.m. was able to reach the learning criterion when at 9 r.p.m.; it accomplished this after six series of trials. Although the number of Hartley able to reach the learning criterion decreased as the rate of rotation increased and the task became more difficult, the number of series needed to achieve the learning criterion by the learners remained the same whatever the rotation rate. If one considers only the animals that learnt the task, the difference in number of series taken to reach the learning criterion by GS and Hartley guinea-pigs was not significantly different both for 3 r.p.m. ($U_{5,6} = 10$, $P > 0.05$) and for 6 r.p.m. ($U_{3,5} = 5$, $P > 0.05$). If one considers all the animals, those that learnt the task and those that did not, the difference between GS and Hartley guinea-pigs was also not significant both for 3 r.p.m. ($U_{5,7} = 10$, $P > 0.05$) and for 6 r.p.m. ($U_{5,6} = 5$, $P > 0.05$). However, if one compares GS and Hartley guinea-pigs for 3 and 6 r.p.m. combined, there was a significant difference between the two groups ($U_{10,13} = 27.5$, $P < 0.05$).

Compared with Hartley, the number of GS guinea-pigs able to reach the learning criterion was greater and they required fewer sessions. The performances of the GS were thus as least as good or if not better than those of Hartley guinea-pigs. While both strains maintained their balance by walking and only very rarely by grasping, there were qualitative differences between GS and Hartley behaviour under these conditions. GS always walked forward perpendicularly to the axis of rotation with their heads directed against the direction of rotation and the body making contact with one of the large disks placed at the end of the rod (always the same disk for a given GS animal). Hartley behaviour was much less stereotyped. They walked along the rotation axis from one end to the other, walked forwards perpendicularly to the rod axis with their heads directed towards the direction of rotation, and, in a few cases, walked backwards

perpendicularly to the rod axis with their heads directed away from the direction of rotation. The fact that it occasionally happened while there was a disturbance in the environment could be that falls of Hartley animals were almost always due to something which happened in the environment, such as a sudden noise in a neighbour room, or movements of the investigator (moving a leg or arm was sufficient to induce a fall), while falls of the GS animals were always due to lack of synchronization of their walking behaviour to the rod's rotation, leading the animals to skid and fall. To examine this assumption further, at the end of the experiment we replaced Hartley and GS guinea-pigs on the rotorod while the environmental disturbances were intentionally elicited and confirmed that the former most often fall when a sudden noise was given or when the investigator raised an arm or only moved his hands, while the latter consistently did not. When falling, GS animals never squeaked, while Hartley often did. All these observations demonstrate that whether the GS guinea-pigs stayed on the rotating rod the same time or even longer than the Hartley guinea-pigs, their motor abilities were worse. Indeed, in spite of their highly stereotyped behaviour, their falls were always due to a lack of motor skills, the falls of the Hartleys occurring when the animals changed their strategy or when an unexpected disturbance occurred in the environment. Moreover, they suggest that the GS animals were less aware of environmental stimulation than Hartleys.

Exploratory behaviour

From the behaviour of the animals during the two familiarization periods it was seen that the Hartley guinea-pigs moved on the floor of the box for 480 ± 115 s while the GS animals remained almost motionless, making only small movements of the head and exceptionally one or two steps. Following the familiarization periods, when the pierced platform was replaced into the box, it was obvious that GS guinea-pigs exhibited also significantly less exploratory behaviour than Hartley guinea-pigs. During the 20 min observation period, GS animals spent no time in the central area of the platform, while Hartley guinea-pigs explored the central area 13.3% of the time (160.2 ± 100.4 s) (Fig. 2A). This difference in behaviour is significant ($U_{6,5} = 2$, $P < 0.05$). During the observation period, GS guinea-pigs walked for 1.7 ± 1.1 s (0.1% of the time) and poked their heads into only 0.7 ± 0.7 holes, while Hartley guinea-pigs walked for 43.2 ± 24.4 s (3.6% of the time) and investigated 9.2 ± 4.2 holes (Fig. 2B). This difference between GS and Hartley exploration is also significant [$t(9) = 3.04$, $P < 0.05$ for walking time and $t(9) = 3.93$, $P < 0.01$ for hole poking].

A similar lack of exploratory behaviour was noticed when the animals were taken from their familiar cage and placed on the floor of the experimental room and observed for several minutes. Under these conditions, Hartley guinea-pigs walked freely while GS guinea-pigs remained exactly where they had been placed (as shown by landmarks surrounding the animals) for 15 min or more.

The lack of exploration of the GS guinea-pigs can be explained either by a decreased motivation to explore a novel environment and/or by the long time required to adapt to the novel environment.

Reactions to auditory stimuli

GS guinea-pigs showed a marked lack of response to pure tones which was not correlated to sound intensity. In the five GS animals tested, exposures to 50, 65, 80 and 95 dBA pure tones gave no response by one or more of the reactions described in the Materials and methods section 50%, 17%, 75% and 50% of the time, respectively (Fig. 3). In contrast, exposures of the six Hartley animals to 50–95 dBA pure tones were associated with no response only

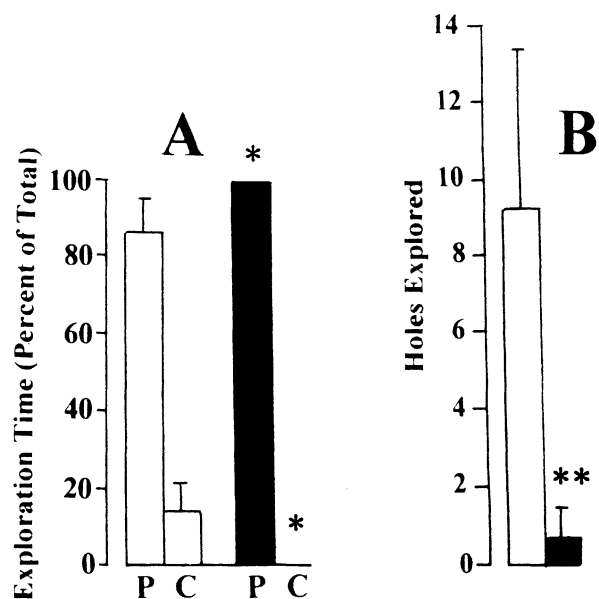


FIG. 2. GS guinea-pigs exhibit less exploratory behaviour in a defined setting than do Hartley guinea-pigs. (A) Mean per cent (\pm SEM) of observation time spent by Hartley (open bars) and GS (filled bars) in peripheral (P) and central (C) areas of exploration platform during 20 min observation period. (B) Mean (\pm SEM) number of holes in experimental platform explored by Hartley (open bars) and GS (filled bars) in a 20 min observation period. Difference in means between Hartley and GS is significant at $*P < 0.05$ and $**P < 0.01$.

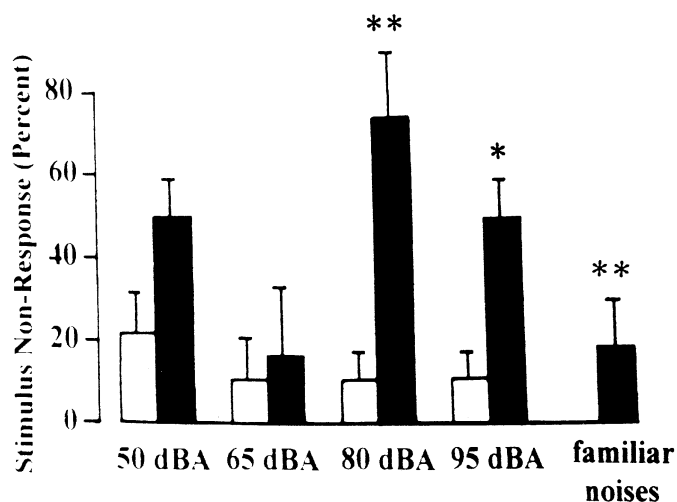


FIG. 3. GS guinea-pigs are less responsive to pure tone and familiar noises than Hartley guinea-pigs. Mean per cent (\pm SEM) of Hartley (open bars) and GS (filled bars) guinea-pigs not responding to auditory stimulus. Difference in means between Hartley and GS is significant at $*P < 0.05$ and $**P < 0.01$.

11–22% of the time. This difference in response is significant for 80 dB [$t(31) = 2.81$, $P < 0.01$] and 95 dB [$t(31) = 2.06$, $P < 0.05$]. Moreover, Hartley always (100%) responded to familiar noises while GS animals responded only 81% of the time to these noises (Fig. 3) [$t(31) = 2.81$, $P < 0.01$]. Whatever the noise intensity, Hartley and GS guinea-pigs exhibited an orientation reaction as well as a jump at the noise onset. However, the escape reaction and the squeaks increased in Hartleys as the intensity of the noise increased, while in GS there was no correlation between the intensity of these two reactions and the intensity of the noise. Indeed, escape reaction and

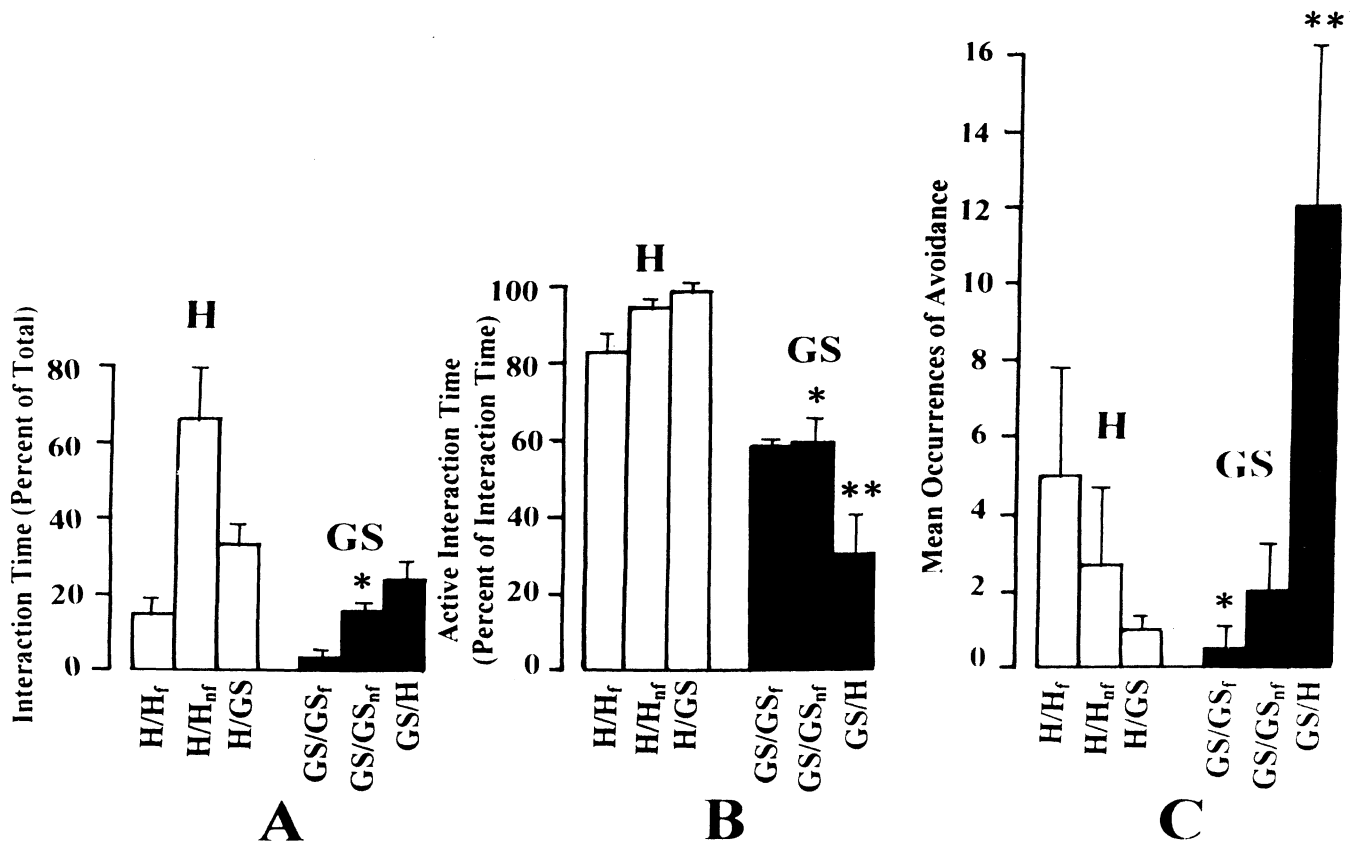


FIG. 4. GS guinea-pigs exhibit less socialization behaviour than Hartley guinea-pigs during a 15 min observation period in a defined setting. A. Mean interaction time (\pm SEM) (per cent of total observation time) by Hartley (open bars) and GS (filled bars) guinea-pigs when another animal was introduced to socialization cage. (B) Mean active interaction time (\pm SEM) (per cent of total interaction time) by Hartley (open bars) and GS (filled bars) guinea-pigs when another animal was introduced to socialization cage. (C) Mean number of avoidances (\pm SEM) by Hartley (open bars) and GS (filled bars) guinea-pigs when another animal was introduced to socialization cage. Animal exposed to a familiar animal (H/H_f or GS/GS_f), or to a non-familiar animal of the same group (H/H_{nf} or GS/GS_{nf}) or of the other group (H/GS or GS/H). Differences in mean responses of Hartley and GS animals are significant at * $P < 0.05$ and ** $P < 0.01$.

squeaks were more frequent at 65 dB than at 80 and 95 dB. Moreover, if Hartley guinea-pigs often stopped eating when the noise was elicited, GS guinea-pigs did not.

Social interactions

Hartley guinea-pigs interacted vigorously with Hartley and GS guinea-pigs under the experimental conditions. During the 15 min observation period, Hartley interacted 15% of the time with familiar Hartley guinea-pigs from the same cage, much more frequently (66% of the time) with unfamiliar Hartley animals from another cage, and only 33% with GS animals (Fig. 4A). Most Hartley interactions with all animals were active ones (83–99% with these three groups) (Fig. 4B).

GS interacted less frequently with other guinea-pigs than did Hartleys, but interactions increased when the animals were different (4%, 16% and 24% of the observation time with familiar GS, non-familiar GS and Hartley, respectively) (Fig. 4A). Active interactions of GS animals were much less frequent than those of Hartley, and accounted for 58–59% of the interaction time with familiar or unfamiliar GS, but only 30% of the interaction time with Hartley (Fig. 4B).

Hartley and GS rarely avoided social contacts with animals belonging to their own group, and Hartley rarely avoided contacts with GS (only a single occurrence as a mean in four experiments lasting 15 min each). GS avoided social contacts with Hartley much more frequently (12 times as a mean in four experiments lasting

15 min each) (Fig. 4C). In Hartley animals, avoidance of social contacts decreased as a function of novelty, while such avoidance behaviour increased in GS animals (Fig. 4C). These differences are significant ($F_{1,6} = 6.42$, $P < 0.05$).

Discussion

In an effort to determine if GS behaviour could represent an animal model of autism, Hartley and GS guinea-pigs were compared in a number of behavioural tests. Compared with Hartley, more GS guinea-pigs reached the learning criterion on the rotating rod and required fewer trials. This would seem to indicate that the learning capabilities of the GS were as least as good or if not better than those of Hartley guinea-pigs. On the other hand, GS differed behaviourally from Hartley in a number of ways. The GS learning pattern showed motor stereotypy. GS animals were inattentive to environmental stimuli in several test situations, they evinced a lack of exploratory behaviour or required a long time to adapt to a novel environment; they also present a variability in response to sounds and a withdrawn attitude. Their social interaction was less than that of Hartley guinea-pigs. They exhibited a small duration of active interaction and frequently avoided interaction with Hartley guinea-pigs in the test situation.

All these behavioural abnormalities have been observed many times in autistic infants. Indeed, motor stereotypy is well-known in autism (Damasio & Maurer, 1978; Golse, 1986; Sauvage *et al.*, 1993)

and studies using auditory event-related potentials and other measures, demonstrating reduced responsiveness to auditory stimuli and responsiveness uncorrelated with sound intensity, have been reported in autistic patients (Bruneau *et al.*, 1987; Bruneau, 1994; Lincoln *et al.*, 1995). Several studies have documented attention control abnormalities in autism and abnormally reduced responsiveness to environmental stimuli and novelty (Courchesne *et al.*, 1984, 1985, 1990, 1994a; Dawson *et al.*, 1988; Bryson *et al.*, 1990; Ciesielski *et al.*, 1990b; Casey *et al.*, 1993; Lincoln *et al.*, 1993; Townsend & Courchesne, 1994; Townsend *et al.*, 1996) as well as social interaction deficit (Kanner, 1943; Curcio, 1978; Mundy *et al.*, 1986, 1990; Sigman *et al.*, 1987; Landry & Loveland, 1988; Dawson & Lewy, 1989). Behavioural responses of GS guinea-pigs resemble those observed in autistic infants (Adrien *et al.*, 1991; Osterling & Dawson, 1994).

As previously mentioned, GS guinea-pigs have cerebellar and cerebrocortical developmental abnormalities (Lev-Ram *et al.*, 1993). GS cerebellum lacks the shallow depressions defining the borders of the vermis. In 3-week-old animals, the extent of folia VI and VII is reduced compared with Hartley; in 1-year-old GS, folium VIII cannot be found and folia VI_a, VI_b, VI_c, VII_a and VII_b are compressed into a single large folium with no distinctive subdivisions. The cerebellum in 3-week-old GS animals had 20–25% fewer granule and Purkinje cells than were present in Hartley cerebellum. Neocortical abnormalities consist of mild shrinkage of neuronal cell bodies, accumulation of neurofilaments in the pyramidal neurons of cortical layer 5 and decrease in dendritic complexity. These alterations are likely to prevent full growth achievement of the structure.

While cortical brain damage has been reported in autistic patients, such as volume loss in parietal lobes bilaterally (Courchesne *et al.*, 1993) and a reduced size of the posterior regions of the corpus callosum where parietal lobe fibres are known to project (Egaas *et al.*, 1995), cerebellar abnormalities have been described considerably more frequently. Williams *et al.* (1980) were the first to report one patient having Purkinje cell loss throughout the cerebellum and meeting the description of autism. Subsequently, a quantification of the Purkinje cells revealed a greater percentage loss in the vermis than in the cerebellar hemispheres in autistic patients (Ritvo *et al.*, 1986). The implication of the cerebellum in autism has also been reported by Bauman & Kemper (1985) who found loss of Purkinje cells and the existence of abnormal neurons in the deep cerebellar nuclei in autistic patients. Hypoplasia of vermal lobules VI–VII seems to be a common finding in the majority of autistic patients as demonstrated for the first time by Courchesne *et al.* (1987, 1988) and later on by a number of authors (Ciesielski *et al.*, 1990a; Courchesne *et al.*, 1994b; Saitoh *et al.*, 1995; Hashimoto *et al.*, 1995). The last authors' study is probably the largest one ever done (as it includes 102 autistic patients and 112 controls) and the first to provide direct evidence that vermis abnormalities in autism are present in the very first year of life. In this connection, it is important to note that the cerebellar abnormalities of GS guinea-pigs involve the same vermal folia VI and VIII (Lev-Ram *et al.*, 1993) reported to be involved in autistic children. It must also be emphasized that, except for a very few studies which have reported limbic anatomical defects in autism (Bauman & Kemper, 1985, 1994; Raymond *et al.*, 1996), none have reported limbic anatomical deficits. Similarly, the GS guinea-pigs did not show any detectable abnormality in the hippocampus (and in the ascending reticular fibres of the brain stem) (Lev-Ram *et al.*, 1993).

The study of autism has also made (and our animal model of autism could make) a contribution to basic knowledge in neuroscience. For about two centuries, the role of the cerebellum was thought to be largely limited to motor control. From two decades, animal studies have demonstrated that the cerebellum is involved in a number of

behaviours such as self-stimulation (Ball *et al.*, 1974), auditory, visual and somatosensory modulation (Crispinio & Bullock, 1984), exploration of a novel environment (Anderson, 1994) and social, emotional and fear responses (Bernston & Schumacher, 1980; Rondi-Reig *et al.*, 1997). These studies and others have led to a new view of the cerebellum (Pellionizz & Llinas, 1982; Hamilton *et al.*, 1983; Botez *et al.*, 1985; Leiner *et al.*, 1986, 1989, 1993; Courchesne, 1987, 1989, 1991, 1995a,b, 1997; Courchesne *et al.*, 1988, 1994a,b; Ivry & Keele, 1989; Lalonde & Botez, 1990; Fiez *et al.*, 1992; Dahhaoui *et al.*, 1992; Lalonde, 1994; Caston *et al.*, 1995). These authors argued that the cerebellum plays a significant part in more complex cognitive functions such as attention to novelty, social attention, learning, memory, perception of time, language and thought. The cognitive function of the cerebellum has been recently confirmed by neuroimaging techniques (Schmahmann, 1991; Kim *et al.*, 1994; Gao *et al.*, 1996; Allen *et al.*, 1997).

In addition to the behavioural abnormalities described in the present paper, adult GS guinea-pigs display a prominent and easily elicited tonic neck reflex and occasionally suffer seizures (Lev-Ram *et al.*, 1993). Their behavioural abnormalities might therefore be related to their cerebrocortical dysfunction. This state of affairs finds its counterpart in patients with autism, where parts of the nervous system other than the cerebellum appear to be involved and the incidence of seizures is increased (Sauvage *et al.*, 1990). Autistic subjects also frequently show persistence of primitive reflexes, a finding which has been suggested as evidence for diffuse cortical brain damage (Minderaa *et al.*, 1985). Damasio & Maurer (1978) have proposed that the autistic syndrome results from dysfunction of neural structures in the mesolimbic cortex, neostriatum, anterior and medial thalamic nuclear groups on the basis of clinical observations, suggesting that nervous structures other than the cerebellum might be implicated in autism. Besides, early abnormal cerebellar morphology is not always associated with autistic symptoms and cerebellar dysfunctions may be associated with other mental pathologies. Indeed, atrophy of the vermal folia VI and VII of the cerebellar vermis has been found in the Fragile-X syndrome (Reiss *et al.*, 1991) and in some psychotic patients (Heath *et al.*, 1982), especially in subjects with schizophrenia (Nasrallah *et al.*, 1981, 1991; Lippman *et al.*, 1982) or with bipolar affective disorders (Nasrallah *et al.*, 1981; Lippman *et al.*, 1982).

In spite of these reservations about the neuropathology of autism, the behavioural abnormalities of GS guinea-pigs, such as the neurological and neuropathological abnormalities of these animals, have much in common with human autism. This suggests that GS guinea-pigs could provide an excellent model for future experimental studies of this poorly understood disease. These include systematic examination of the effects of nerve growth factors and substances which interfere with synaptic mechanisms at the cerebellar level (such as GABAergic molecules or *N*-methyl-D-aspartate agonists) on autistic-like behaviour. The availability of an animal model of autism also opens the door to rigorous evaluation of the effects of environmental stimulation ('enriched' environments) on the behavioural expression of the neurophysiological and neuropathological deficits present in GS animals.

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