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Article

Hybrid vigour and hybrid dysgenesis

The effect of early in life enrichment of living conditions

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The formation of a hybrid phenotype in mammals remains a mystery. In order to resolve this mystery we have chosen inbred mouse strains C57BL/6J and DBA/2J, and their F_1 hybrid B6D2F1, took only females for experiment and housed them during postnatal days P22-P60 either in standard or enriched living conditions, always 4 mice per cage. This adolescent cage enrichment has evoked either induction of hybrid vigour or its significant enhancement, observed in different operant behavioural tasks during the rest of their life (Morris water maze, Go/NoGo sound frequency and sound duration discrimination tasks). This induction or enhancement can be understood only if ontogenesis is an active process, driven by action acceptors – by entities that percept the achievement of positive developmental results, even if the last ones have appeared with a help of random or unexpected factors of stochastic or genetic nature. The same way action acceptors direct evolution on Earth.

The term "hybrid vigour" defines all superior attributes of a hybrid organism in comparison with similar gender representatives of both parental lines[1-2]. The term "hybrid dysgenesis" defines the opposite – all inferior attributes of an organism in comparison with both parental lines (pp. 76-77[3], 156[3]). Hereinafter we use the word "strain" for inbred laboratory animals (*e.g.* C57BL/6J and DBA/2J mice), the word "stock" – for outbred ones (*e.g.* NMRI mice, Wistar rats, albino and multi-coloured guinea pigs), the word "line" is used to describe both inbred and outbred laboratory animals together, as well as all intermediates, in accordance with recommendations of ICLA-72. The term "good stock" is applicable to healthy outbred laboratory animals, those are good breeders and, as a rule, females from such stock can be used as foster mothers.

Hybrid vigour is typically observed if we have two inbred strains as parents; hybrid vigour is typically expressed as increased body weight and increased "strength" (a bit subjective term, but F_1 hybrid mice in fact can survive in semi-natural outdoor conditions, wherein parental inbred strains cannot survive a winter)[4]. Hybrid dysgenesis is typically observed if we have chosen both parents from two good outbred stocks; hybrid dysgenesis is expressed as decreased lifespan together with various health-related issues, appearing during aging and/or detectable early in life. Among such health-related issues there are over-reaction of immune system, allergies, up to various auto-immune diseases (dogs, cats, guinea pigs), problems with digestive system (dogs, cats, guinea pigs), problems with nervous system (guinea pigs; *e.g.* semi-spontaneous seizures, resembling audiogenic ones), problems with reproductive system (cats, *e.g.* Bengal cats – F_1 and F_2 infertility in males). Bengal cats are becoming more and more popular today as pets, and their F_1-F_4 generations can serve as a good illustration of hybrid dysgenesis in mammals, but the same or about the same hybrid dysgenesis is observable in guinea pigs at much low cost.

Two brief conclusions concerning hybrid dysgenesis – one practical and one theoretical: 1) hybrid dysgenesis is evident in species those whole lifespan is practically accessible, and laboratory mice and rats do not belong to this category; 2) hybrid dysgenesis is expressed as problems in regulation in one or several functional systems, these problems can be expressed differently in different subjects of the same cross and sometimes

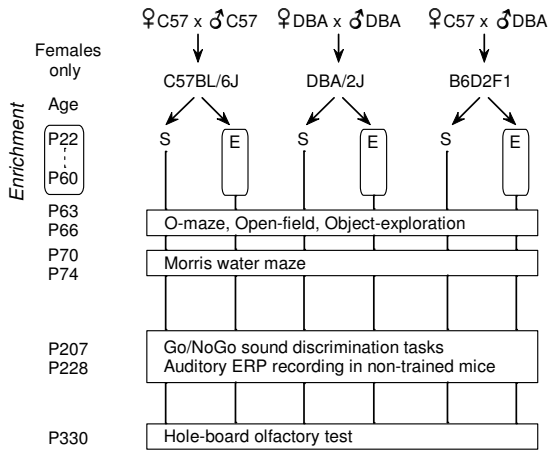

Figure 1 | Breeding paradigms, cage enrichment and behavioural tests. Female mice (strains C57BL/6J, DBA/2J & their F_1 hybrid B6D2F1) were housed during postnatal days P22-P60 either in the cages "Type 2a" (365 × 207 mm) – "Standard" or in the cages "Type 4" (595 × 380 mm) with different toys renewed twice weekly – "Enriched"; always 4 mice per cage.

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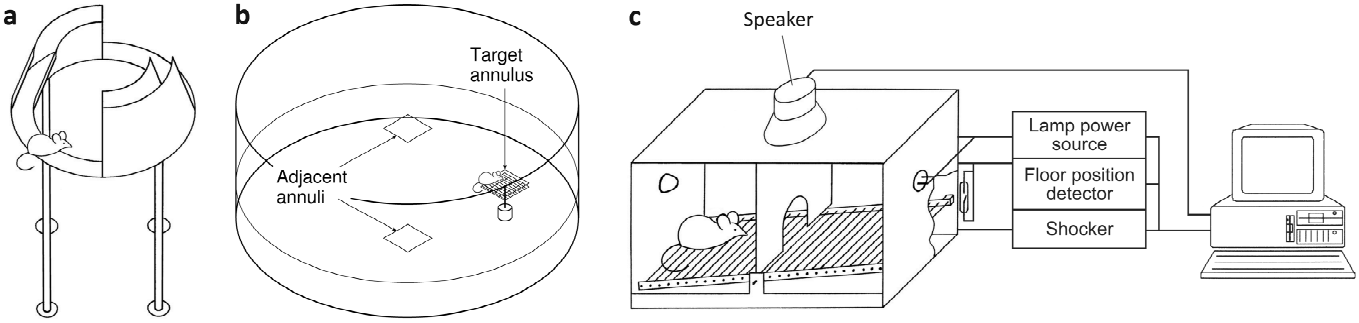

Figure 2 | Equipment for behavioural tests. (**a**) Elevated 0-maze (D = 46 cm, elevation h = 40 cm; 5 min test). (**b**) Morris water maze (d = 150 cm, walls H = 50 cm from the bottom; water level (+ 1 L of milk) h = 15 cm; platform 14 × 14 cm placed 0.5 cm below the surface; annulus – square 16 × 16 cm). The mice performed 16 training trials in 4 days (4 daily, max. duration of each trial 90 s, with an inter-trial interval of 30 s spent on the platform – massed training). On day 5, the mice performed a 60 s probe test without the platform. (**c**) Go/NoGo sound discrimination task (box 270 × 115 × 130 mm with two parts; arch opening 38 × 49 mm) had 40 Go and 40 NoGo daily trials with 7 training days for both sound frequency and duration discrimination tests.

it is practically impossible to discriminate between primary and secondary problems in different affected systems of one animal. Animals of the same cross can demonstrate very different abnormalities and during lifespan of a single individual an abnormality can be sometimes expressed stochastically in all-or-none fashion, *i.e.* it can be unstable in time.

Traditional explanation of hybrid vigour is based on mechanistic interaction of previously dissociated genetic elements, whereas the unstable and destabilized expression of hybrid dysgenesis is pointing out to epigenetic mechanisms[5-8]. If epigenetic interactions have prevailing influence on hybrid phenotype, then its ontogenesis should be sensitive to external influences. In order to test this opportunity we have chosen two inbred mouse strains: C57BL/6J and DBA/2J, and their F_1 hybrid B6D2F1, obtained from cross: ♀C57BL/6J × ♂DBA/2J.

We have selected only females due to practical reasons (the absence of fights) and placed one half of them into enriched living conditions[9] at P22 (one day after weaning) and they were removed from the enrichment at P60, three days before the beginning of behavioural tests (P63) – thus, the whole adolescent period was included into the P22-P60 enrichment period (**Fig. 1**).

Sometimes such cage enrichment is thought as a tool that makes life of a mouse closer to the wild nature. In wild mouse populations (*e.g. Apodemus sulvaticus*), both in the USA (upstate NY) and Russia (Tver region), a lifespan of a mouse is terminated by an interaction with an aerial or terrestrial predator, and the rate of reproduction is determined by food availability, which is always scanty (mammals are horny when they are fed *ad lib*; when they are not fed *ad lib*, they are not so horny). A wild-caught mouse has big head (in comparison with laboratory one), attached to under-developed body, because it needs brain to predict the appearance of a predator, and it has small body due to malnutrition, because any search for food is risky. In a laboratory mouse the lifespan is not determined by an interaction with a predator and the rate of reproduction is not limited by food availability. Thus, we are using cage enrichment only as a tool to reactivate some epigenetic mechanisms.

Elevated 0-maze was the first test that was applied after the end of enrichment period (**Fig. 1**). This test measures the anticipation of an interaction with an aerial and/or terrestrial predator in the particular environment by a mouse (**Fig. 2a**, **Fig. 3a**). Hybrid non-enriched mice have the strongest anticipation of

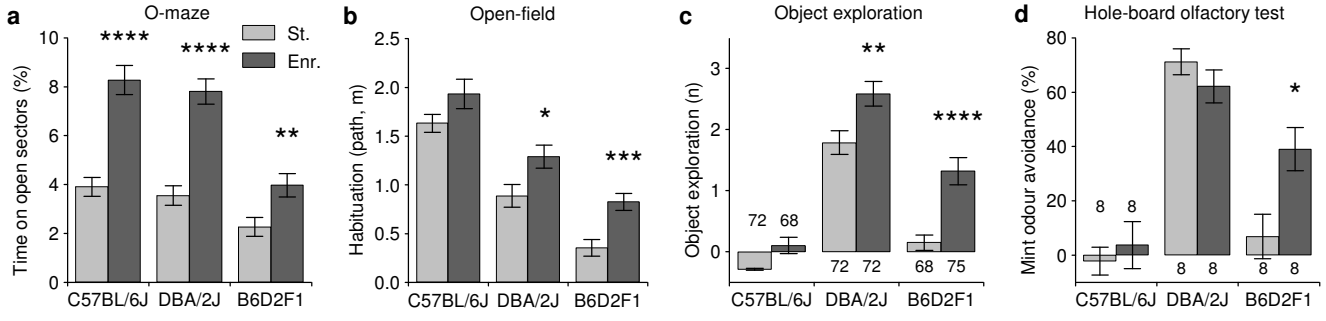

Figure 3 | Exploratory behavioural tests. (**a**) Elevated 0-maze. (**b**) Open-field (arena 50 × 50 cm, wall h = 37 cm; 30 min). "Habituation (path, m)" – the difference in the path travelled between the first and the last 10 min. (**c**) Object exploration (the same arena) – 24 h after the open-field test the animals were tested during 30 min once again, but during the last 15 min a semi-transparent 50 ml Falcon tube (h = 12 cm, d = 4 cm) was placed vertically in the centre of the arena. "Object exploration (n)" – the difference in the number of small movements in the object zone between the last and the first 15 min. (**d**) Hole-board olfactory test (arena 40 × 40 cm, 16 holes d = 2.5 cm, wall h = 32 cm). This test was done after usual hole-board test without odour that consisted of 3 days, one 6-min session daily. During the fourth day under the one half of the floor a dry Mint powder was added. Mice avoid Mint odour. Avoidance (%) was calculated during 6-min session using total exploration time of holes with (O) and without (NO) odour: ((NO – O)/(NO + O)) × 100. Hereinafter: asterisk, $P < 0.05$; double asterisk, $P < 0.01$; triple asterisk, $P < 0.001$; quadruple asterisk, $P < 0.0001$. Mann-Whitney U-test. Mean ± SE.

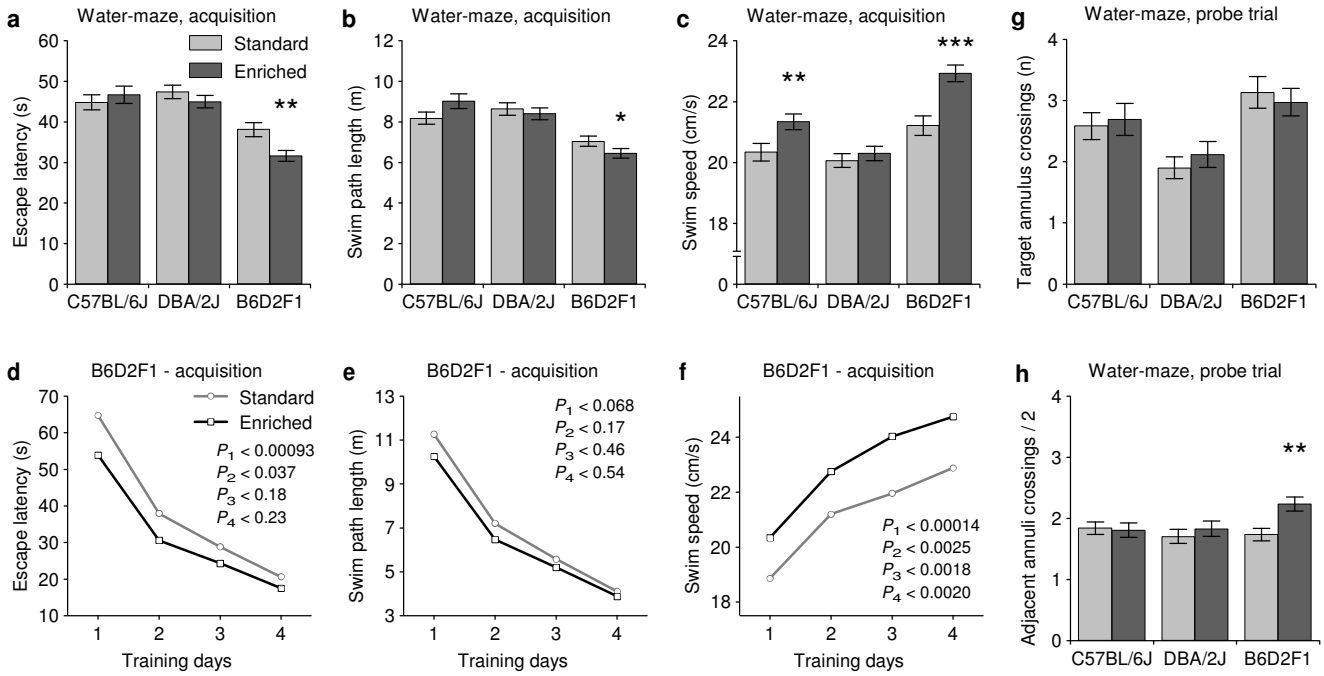

Figure 4 | Morris water maze. (**a**-**c**) Mean values of four training days. (**d**-**f**) Mean values of each training day separately for hybrid B6D2F1 mice. Similar values for inbred C57BL/6J and DBA/2J mice are shown in the **Supplementary Fig. 4**. (**g**-**h**) Probe trial (60 s without platform, day 5). Note that during the probe trial, the hybrid mice have shown the increased number of adjacent annuli crossings – however the platform was never placed here and it is not the memory, but the anticipation of the future – the mice believe that the platform should be here with higher probability than in other places. Mice never had material evidence for such anticipation, but nevertheless their idea leads to better overall performance (**a**) and shorter swim path (**b**).

such a dangerous event (**Fig. 3a**, the shortest bar). The enrichment does decrease the anticipation of an interaction with a predator in both inbred mouse strains, with very high statistical significance (**Fig. 3a**, the two longest bars), but the same enrichment only slightly potentiates such potentially dangerous behaviour as the presence on open sectors in hybrids, and the enriched hybrids finally show the same anticipation of a predator as non-enriched inbred mice (**Fig. 3a**, the most right bar). Thus, if the effect of enrichment is potentially dangerous – it is minimal in hybrids, and it looks like the effect of enrichment is controlled by a prediction from the side of a mouse.

In the next test (Open field) the non-enriched hybrids demonstrate the slowest habituation (**Fig. 3b**), but the effect of enrichment is the most pronounced in these animals. After the introduction of a new object into this open field (**Fig. 3c**), we can see that the enrichment has converted B6D2F1 phenotype from C57BL/6J-type into DBA/2J-type. All three above-mentioned tests were done soon after the end of enrichment period (**Fig. 1**), and here the effects of enrichment could be considered as "temporal", but not "ontogenetic" (they are, in fact, ontogenetic, but we cannot say this on the basis of these three tests).

The olfactory test with Mint odour avoidance was done 9 (nine) months after the end enrichment period. During all these 9 months all animals were housed in standard cages. Nevertheless, the Mint odour avoidance was converted in the hybrid mice from C57-type towards DBA-type (**Fig. 3d**). Statistical significance is not very high here, because we have 8 mice in each group only, contrary to 9 independent batches [each with 8 mice per group] in early tests [0-maze, Open field, Object exploration and Morris water maze], wherein n = 72, 68, 72, 72, 68, 75 (**Fig. 3c**).

The interpretation of all exploratory tests, with some exception of 0-maze, is always controversial, because it is unclear which type of behaviour is "better"; there are no objective means to discriminate between the "superior" and the "inferior". We have chosen two operant behavioural tasks with negative reinforcement – Morris water maze (**Fig. 2b**) and Go/NoGo sound discrimination task (**Fig. 2c**) – those provide clear distinction between "good learners" and "bad learners".

In the Morris water maze all mice have to learn how to find a platform, covered by water made opaque by an addition of milk (**Fig. 2b**), using several trials. The presence in the water, despite it is not very cold, is aversive for a mouse and the mouse would like to find a platform as soon as possible. The escape latency serves as a main indicator of performance (**Fig. 4a**). Classical hybrid vigour is evident without any enrichment (**Fig. 4a**, the light bars), whereas the enrichment has developed the existing hybrid vigour even further, but the positive effect of enrichment was evident only in hybrids, but not in the inbred mouse strains (**Fig. 4a**, the dark bars).

The improvement of performance by means of early in life enrichment was possible only for hybrids. The enriched hybrids had not only shorter escape latency (**Fig. 4a**), but shorter swim path length (**Fig. 4b**). The enriched hybrids had also increased swim speed, observed during all four training days, and it cannot be explained by slightly shorter swim path length due to relatively high statistical significance of the increased swim speed (**Fig. 4c**). The swim speed was also slightly improved by the enrichment in the inbred C57BL/6J mice (**Fig. 4c**), but no other enrichment effects were observed in the Morris water maze in the inbred mice.

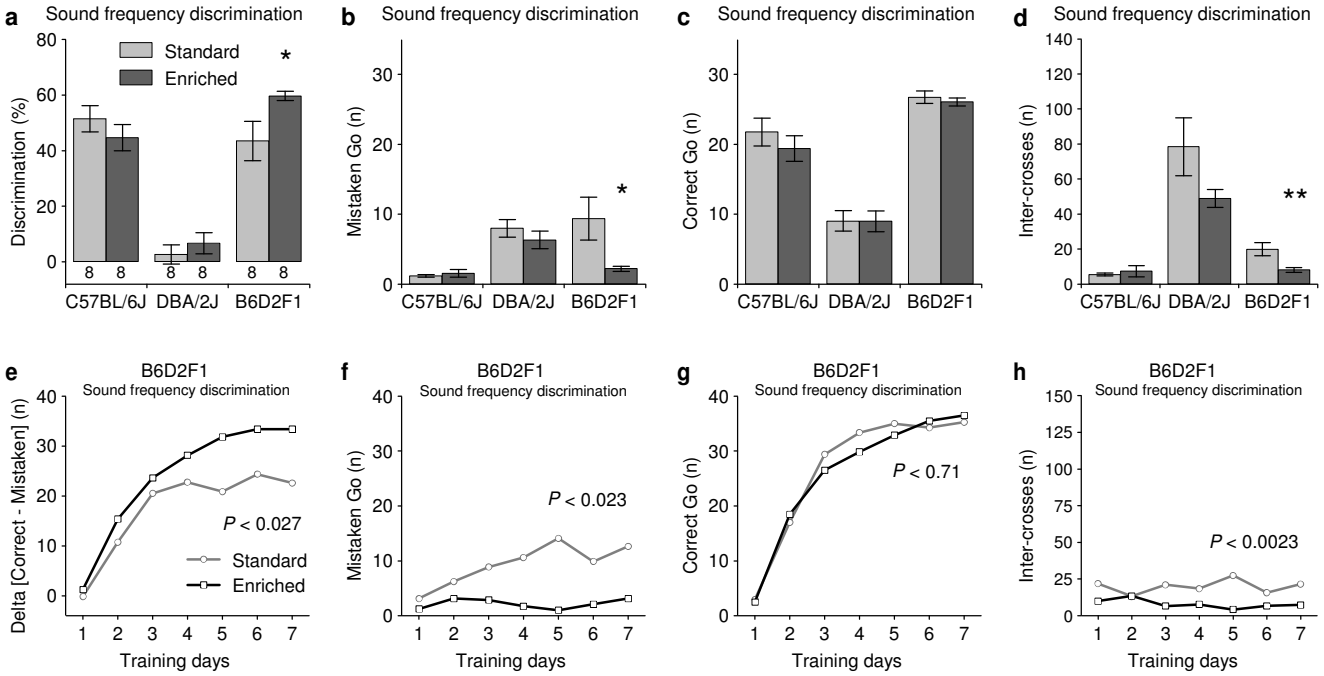

Figure 5 | Go/NoGo sound frequency discrimination task. "Go" signal consisted of two sounds: 50 ms 2.5 kHz and 50 ms 10 kHz, which were separated by 200 ms of silence. "NoGo" signal consisted of two identical 50 ms 5 kHz sounds separated by 200 ms of silence. Each "Go" trial consisted of 5 "Go" signal presentations with inter-signal interval 1 s (onset-to-onset). But if the animal did not move to the opposite compartment, it received additional "Go" signal presentations (maximum 5), paired with negative reinforcement – with electric current, 200 ms, 0.20 mA. Each "NoGo" trial consisted of 5 "NoGo" cue presentations. If the animal was moving to the opposite compartment during these 5 sec, it received negative reinforcement – current 200 ms, once.

It is interesting to note that simple combinatorial model of hybrid vigour is not working for the results of Morris water maze: if some genetic elements were randomly fixed in the C57BL/6J genome, and some others – in the DBA/2J genome, and if they were combined together in the B6D2F1 hybrid like a key-lock interaction, then we should expect to see already full hybrid vigour in the non-enriched hybrids, and the enrichment should be able to do nothing for its further improvement.

The second mystery is that we can see specifically the improvement, but not the degradation of performance in all hybrids (both enriched and non-enriched). The fixation of genes in an inbred strain is basically a stochastic (random) process, with negligible effect of natural and artificial selection. And it is statistically impossible that two randomly selected groups of genes being combined together in hybrids will produce superior functional system without a help of any purposive activity (at least, with the same probability the effect will be negative as well as positive). These two arguments lead us to the assumption that the development of hybrid vigour, as well as ontogenesis in general, is an active and purposive process.

During the probe trial the platform was removed from the tank for the whole 60 seconds of testing and all mice were searching for it without any positive result. No effect of enrichment was observed here (**Fig. 4g-h**), except one curious observation: the number of adjacent annuli crossings was significantly higher for enriched hybrids than for all other mice (**Fig. 4h**). Usually water maze is classified as a test for spatial memory. However the enriched hybrid mice have demonstrated here not "better memory" (the platform was never placed into the adjacent annuli for any given mouse), but "better anticipation" of the future.

The fact that the individual behaviour of an animal is driven by an anticipated future has been recognized by Peter K. Anokhin many years ago (before the World War II), on the basis of his experiments with dogs. The term "action acceptor" was introduced by Peter K. Anokhin in 1955[10-11] to describe the entity that senses the appearance of the anticipated result (typically – positive result – the animal is in search for this result). An action acceptor plays similar role in ontogenesis, including early ontogenesis: if a group of cells is in search for some result that could be, for example, some mechanical tension of cell layers in early ontogenesis, as soon as this result is achieved/sensed by a sufficient number of cells, the rest of the cells and/or the cells that have achieved the above-mentioned result are switching their efforts to search for the next anticipated ontogenetic result.

Action acceptors, as well as other components of phenotype, can be partially genetically determined, partially learned or induced by local or external environment of the organism or environment of given cell group. The most important thing is that not only ontogenesis, controlled by a sequence of action acceptors, becomes more robust to external and internal disturbances (to so-called "developmental noise"), but the results of ontogenesis can be improved by unexpected events[12]; the ontogenesis can utilize or it can extract unexpected benefits from random/stochastic developmental deviations and from the appearance of new unexpected entities in the genome of this organism. Exactly the same new/unexpected genetic entities are present in the hybrid genome. The functionality of the ontogenesis of Metazoa is based on the action acceptors to the extent that without developmental noise (variability in the

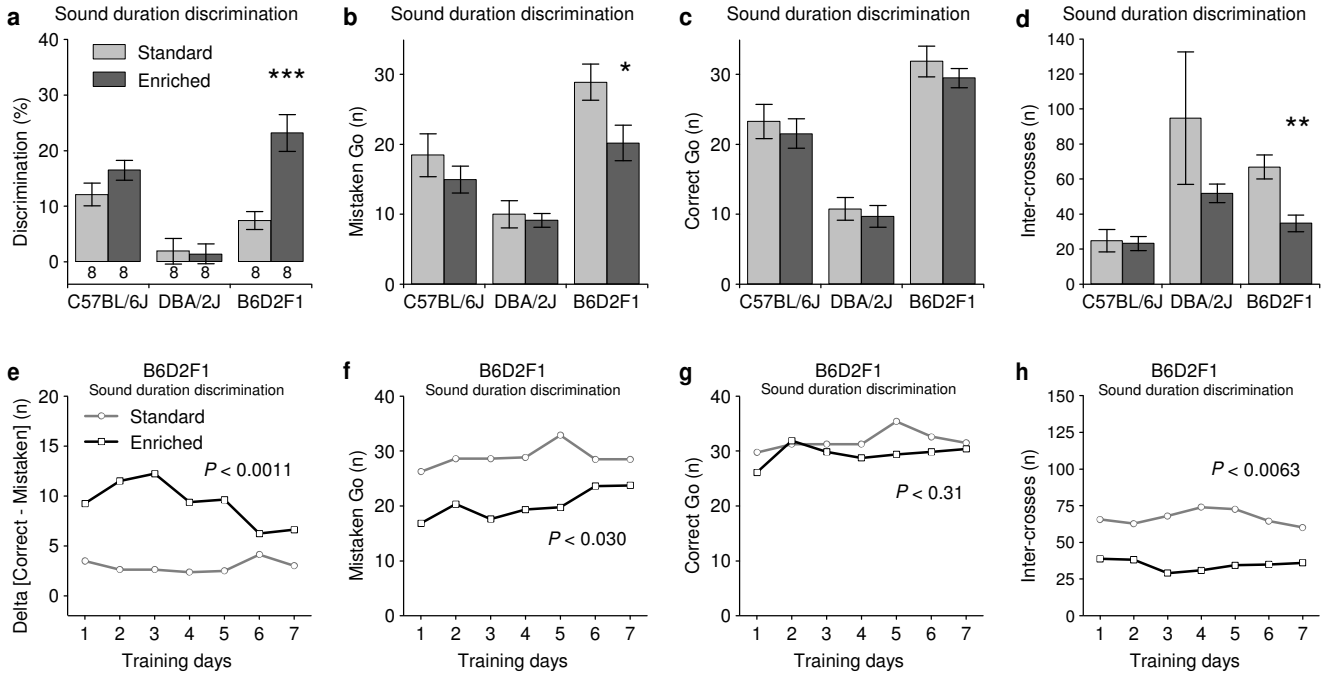

Figure 6 | Go/NoGo sound duration discrimination task. After Go/NoGo sound **frequency** discrimination task (**Fig. 5**), wherein animals were trained during 7 days (40 "Go" and 40 "NoGo" trails daily) to discriminate pairs of sound 5-5 kHz and 2.5-10 kHz, and 7 days of task-free period, the same animals were trained in Go/NoGo sound **duration** discrimination task, also during 7 days (40 "Go" and 40 "NoGo" trails daily). "NoGo" signal was taken from the sound frequency discrimination task. "Go" signal consisted of two sounds: 50 ms 5 kHz and 150 ms 5 kHz, separated by 200 ms of silence. An animal should be able to discriminate the duration of the second sounds – 150 ms in "Go" and 50 ms in "NoGo". This is a very difficult task for all mice.

individual behaviour of the cells that is not genetically fixed) the ontogenesis as a process becomes impossible (Supplementary Fig. 9[13]). And, in principle, the same anticipated result can be achieved by different ways, of course. That is why we have remarkable individual variability in human brain functional morphology (fields, *etc.*).

Go/NoGo sound discrimination tasks, as well as all other Shuttle-box-based tests, were always criticized for being non-ecological for a mouse. During this task mouse learns to go from one compartment to another one during presentation of one sequence of sounds and it learns to stay in the same compartment during presentation of another sequence of sounds, whereas during the absence of any sound sequence presentation the mouse can change compartments freely. Despite the absence of any analogues of this task in the wild nature, the enriched hybrids show superior performance with respect to all other mice in both sound frequency (**Fig. 5a**) and sound duration (**Fig. 6a**) discrimination. In both tasks the enriched hybrids have significantly decreased number of mistaken Go in comparison with non-enriched hybrids (**Fig. 5b,f**, **Fig. 6b,f**) It seems that only the early in life enrichment makes hybrid vigour evident in this Go/NoGo sound discrimination task (*i.e.* no hybrid vigour without enrichment; **Fig. 5a**, **Fig. 6a**), and this test was done 5 (five) months after the end of 38-day enrichment period (**Fig. 1**). How on Earth a random combination of genetic factors plus adolescent enrichment entails superior performance in absolutely

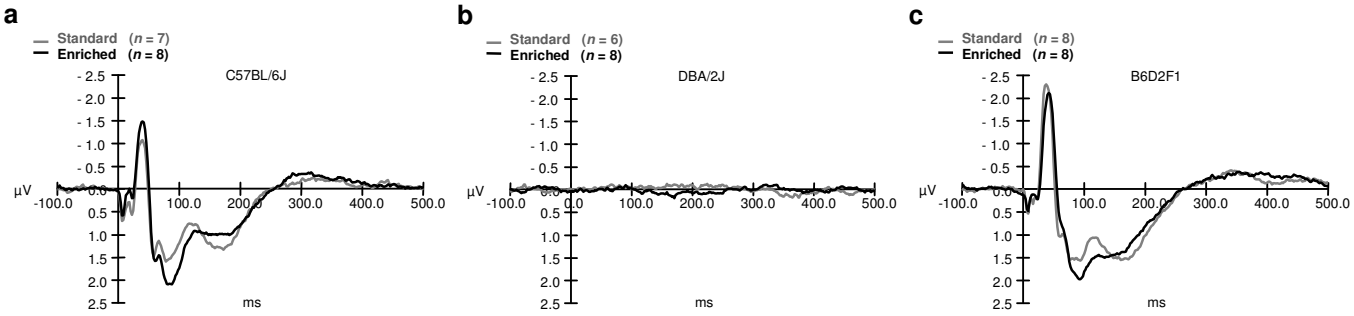

Figure 7 | Auditory evoked potentials. The record was done from the surface of primary auditory cortex in Standard and Enriched C57BL/6J, DBA/2J and B6D2F1 mice. These mice were never trained in Go/NoGo sound discrimination paradigm. This is a grand-average of four paradigms, wherein the stimuli had duration either 50 or 150 ms and consisted of accords either 3 + 6 kHz or 4 + 8 kHz with inter-stimulus interval (onset-to-onset) 500 ms. Note that the enrichment did not change the amplitude of N1 (25 - 50 ms) and produced non-significant similar alterations in P2 (50 - 200 ms) in C57 and F1.

non-ecological task (**Fig. 6a**)? It remains a mystery, unless there are action acceptors which can consolidate functional systems from unexpectedly available components. Sometimes functional systems are thought to be some systems with feedback loops (after cybernetics), wherein the current process is manipulated from the side of the action acceptor in order to achieve the positive result, detectable by the above-mentioned action acceptor. However the described above function of an action acceptor is deeply secondary: feedback can be weak, feedback can be strong, feedback can be absent at all and the positive result can be achieved randomly, but as soon as it is achieved the system is switching to the search for the next ontogenetic result – that is the main function of an action acceptor.

Note that the enriched hybrids have decreased number of inter-crosses in comparison with non-enriched ones (**Fig. 5d,h**, **Fig. 6d,h**), *i.e.* they have decreased spontaneous locomotor activity, whereas in Morris water maze they always have increased swim speed in comparison with all other animals (**Fig. 4s,f**), *i.e.* they have enhanced locomotion. These observations cannot be explained together, unless we are dealing with purposive behaviour in both cases.

If ontogenesis is under significant control of action acceptors those are at least partially heritable and are at least partially genetically fixed, the same action acceptors must be active on the evolutionary time-scale, the same action acceptors are directing evolution. If from a randomly available pool of genetic components some can be activated to serve as a reminder about action acceptor, or to serve as its part, or to comprise the action acceptor as a whole, then evolution becomes internally purposive (as well as ontogenesis currently is) and Darwinian natural selection occurs to be a process of minor importance.

Any action acceptor contains in itself the part that is an anticipated future, and this part is not material at the particular time point of the existence of this action acceptor (**Supplementary Fig. 1**). Here we are at the border of the contemporary natural sciences, at the border between vulgar materialism and religious idealism, and further discussion can be placed only in the **Supplementary Information**.

Methods

Freshly weaned females (C57BL/6J, DBA/2J & B6D2F1) were ordered from Taconic M&B A/S, Ry, Denmark. Received mice had the following body weights: C57BL/6J: 9.71 ± 1.65 g; DBA/2J: 9.33 ± 2.16 g; B6D2F1: 9.96 ± 1.76 g (mean ± SD), corresponding well to P21-P22. Upon arrival (on Tuesday), animals were weighed and ear-marked and assigned in groups of 4 of the same genotype to either standard or enriched housing. Mice were housed under standard and enriched conditions during postnatal days P22-P60 in temperature (21±1°C) and humidity (50±5%) controlled conventional colony rooms under reversed 12-12 h light-dark cycle (lights on at 19:00 h) with water and standard rodent pellets ad libitum. Standard housed mice were kept in "Eurostandard Type II L" cages (365 × 207 × 140 mm; polycarbonate, transparent; "L" means "long"; these cages are also known as "Type 2a") with sawdust as bedding. Enriched housed mice were kept in "Eurostandard Type IV" cages (595 × 380 × 200 mm; polycarbonate, transparent; known also as "Type 4") with sawdust as bedding and a "Mouse House" (Tecniplast, Indulab, Gams, Switzerland) as shelter. In addition, twice a week (Tuesdays and Fridays), one enrichment item (autoclaved) was added to the enriched cages. Enrichments added on Tuesdays (when also new cages with fresh sawdust were provided to all mice) remained in the cage for one week until the next cage change (they were so-called "soft enrichments").

Enrichments added on Fridays remained in the cage until the end of the housing period ("hard enrichments"). Soft enrichments included a soft paper tissue (wk 1), a coarse paper tissue (wk 2), a handful of straw (wk 3), a handful of shredded paper in stripes (wk 4), a handful of pieces of bark (wk 5), and a handful of rodent pellets that were hidden in the sawdust (wk 6). Hard enrichments included a wooden tunnel (25 cm long, inner diameter: 4 cm) with several holes (wk 1), a trapeze (12 cm long, diameter: 1 cm) hung from the cage lid (wk 2), three wooden branches (ca. 30 cm long, wk 3), a cardboard roll (15 cm long, diameter: 4 cm, wk 4), and a cardboard house "Shepherd shack" (Shepherd Speciality Papers, Indulab, Gams, Switzerland, wk 5). Thus, enrichment was a combination of more space, additional resources, increased environmental complexity, and novelty (novel items and environmental change). On the last Friday (wk 6), mice from enriched cages (Type 4) were placed in standard cages (Type 2a) until testing started on the following Monday.

Behavioural testing and other procedures are described in **Supplementary Methods**.

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Additional information

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