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Article

Hybrid vigour and hybrid dysgenesis

The effect of early in life enrichment of living conditions

Dmitri L. Vyssotski[1,2,3]

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

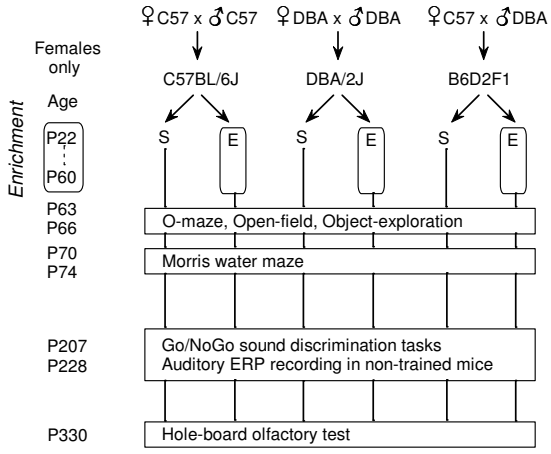

Figure 1 | Breeding paradigms, cage enrichment and behavioural tests. Female mice (strains C57BL/6J, DBA/2J & their F_1 hybrid B6D2F1) were housed during postnatal days P22-P60 either in the cages "Type 2a" (365 × 207 mm) – "Standard" or in the cages "Type 4" (595 × 380 mm) with different toys renewed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

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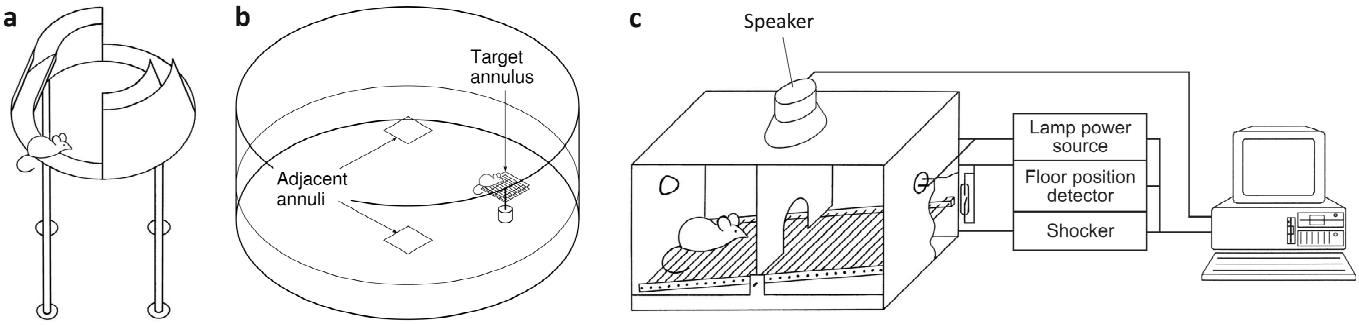

Figure 2 | Equipment for behavioural tests. (**a**) Elevated 0-maze (D = 46 cm, elevation h = 40 cm; 5 min test). (**b**) Morris water maze (d = 150 cm, walls H = 50 cm from the bottom; water level (+ 1 L of milk) h = 15 cm; platform 14 × 14 cm placed 0.5 cm below the surface; annulus – square 16 × 16 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

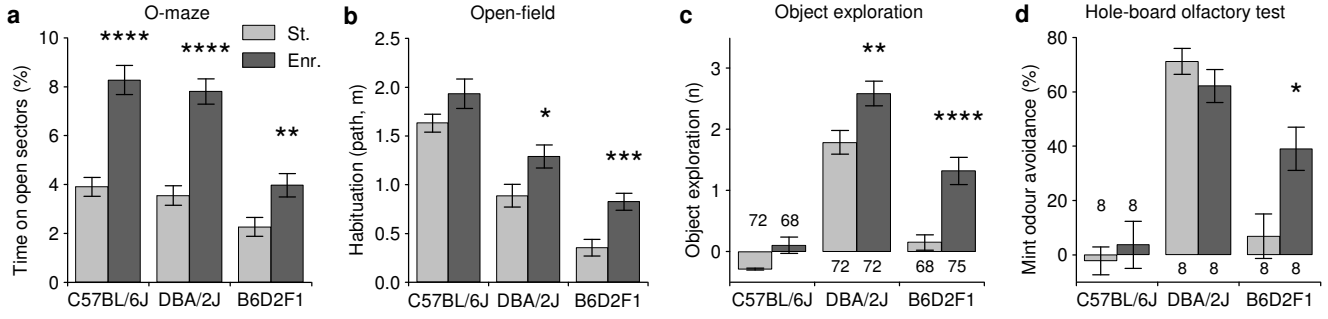

Figure 3 | Exploratory behavioural tests. (**a**) Elevated 0-maze. (**b**) Open-field (arena 50 × 50 cm, wall h = 37 cm; 30 min). "Habituation (path, m)" – the difference in the path travelled between the first and the last 10 min. (**c**) Object exploration (the same arena) – 24 h after the open-field 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.

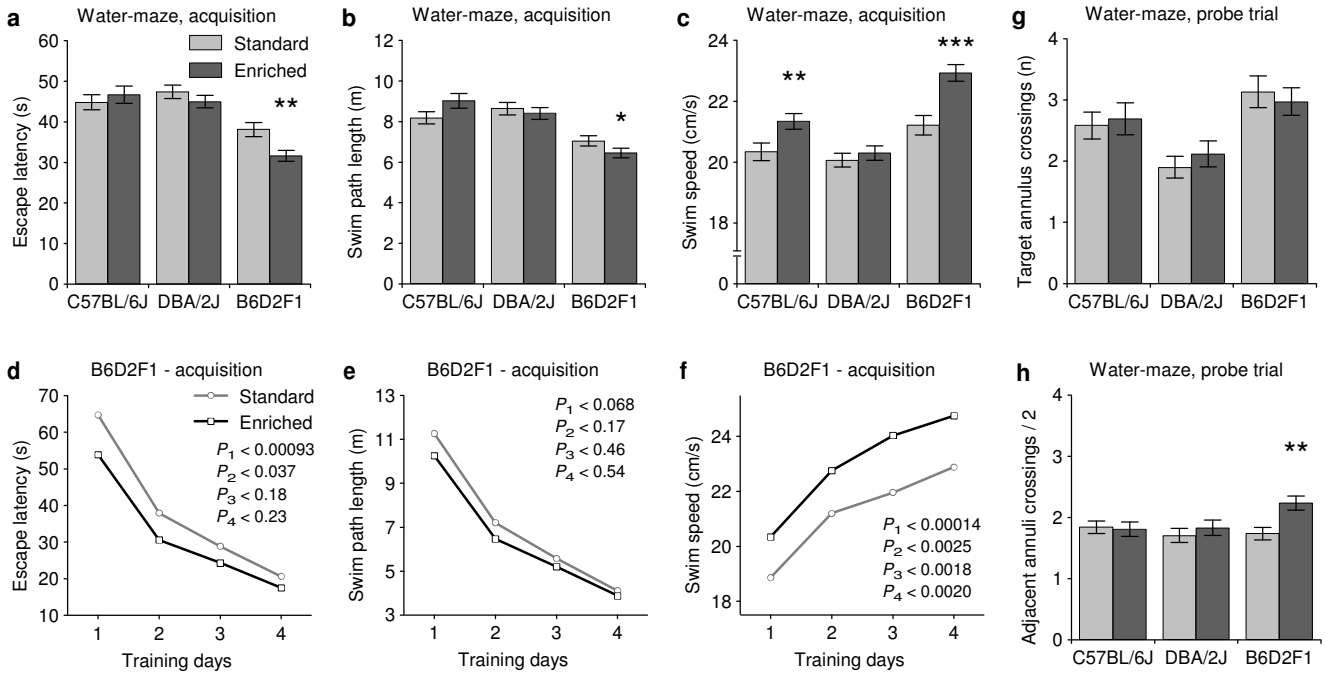

Figure 4 | Morris water maze. (**a**-**c**) Mean values of four training days. (**d**-**f**) Mean values of each training day separately for hybrid B6D2F1 mice. Similar values for inbred C57BL/6J and DBA/2J mice are shown in the **Supplementary Fig. 4**. (**g**-**h**) Probe trial (60 s without platform, 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.

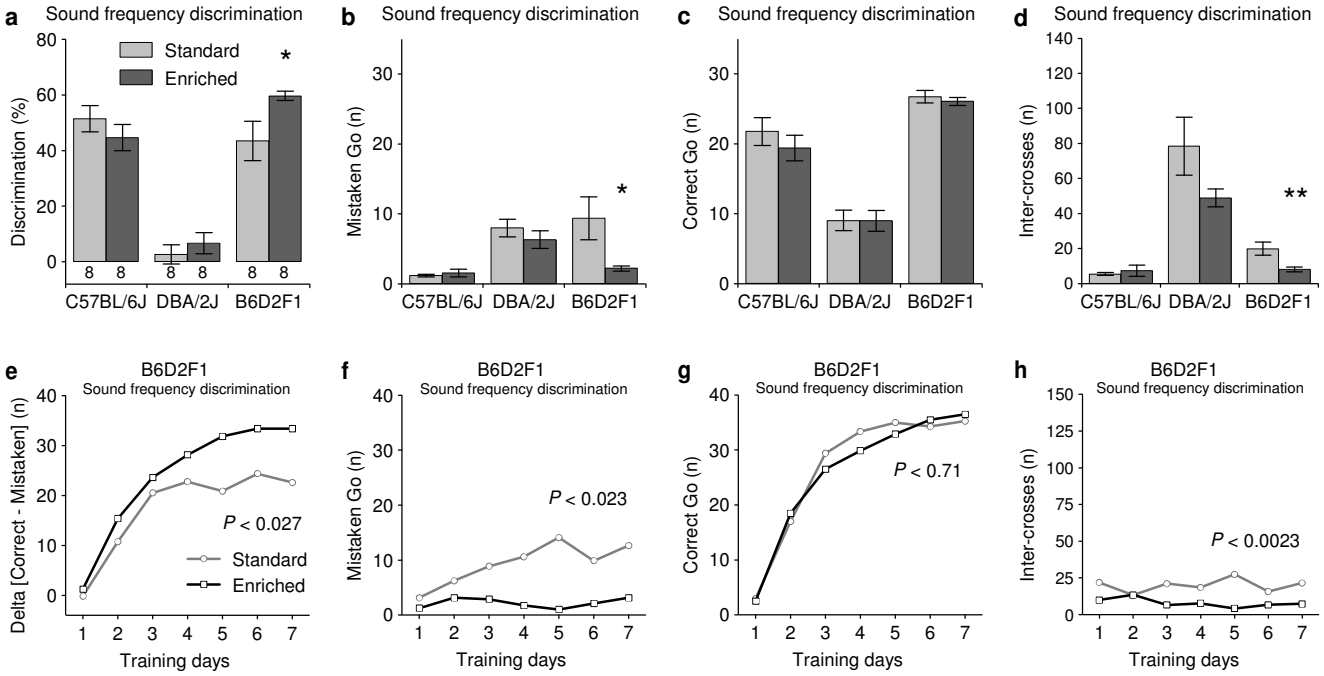

Figure 5 | Go/NoGo sound frequency discrimination task. "Go" signal consisted of two sounds: 50 ms 2.5 kHz and 50 ms 10 kHz, which were separated by 200 ms of silence. "NoGo" signal consisted of two identical 50 ms 5 kHz sounds separated by 200 ms of silence. Each "Go" trial consisted of 5 "Go" signal 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

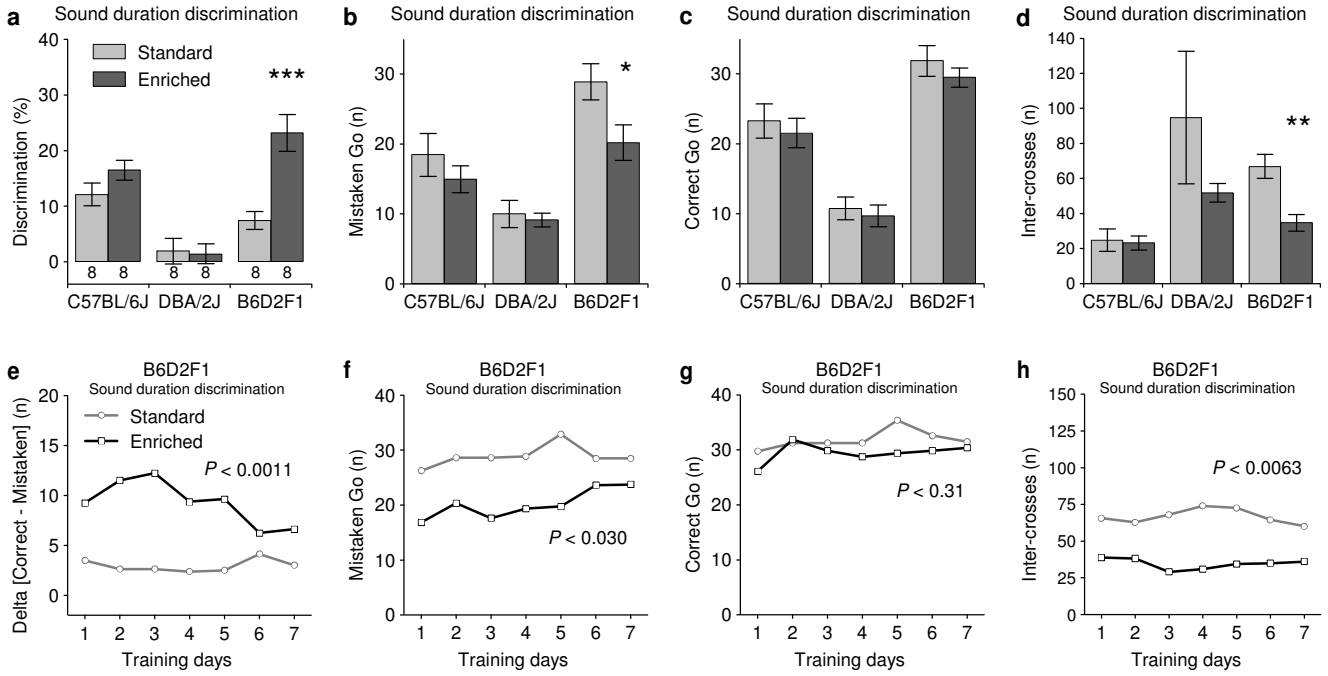

Figure 6 | Go/NoGo sound duration discrimination task. After Go/NoGo sound **frequency** discrimination task (**Fig. 5**), wherein animals were trained during 7 days (40 "Go" and 40 "NoGo" trails daily) to discriminate pairs of sound 5-5 kHz and 2.5-10 kHz, and 7 days of task-free period, the same animals 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

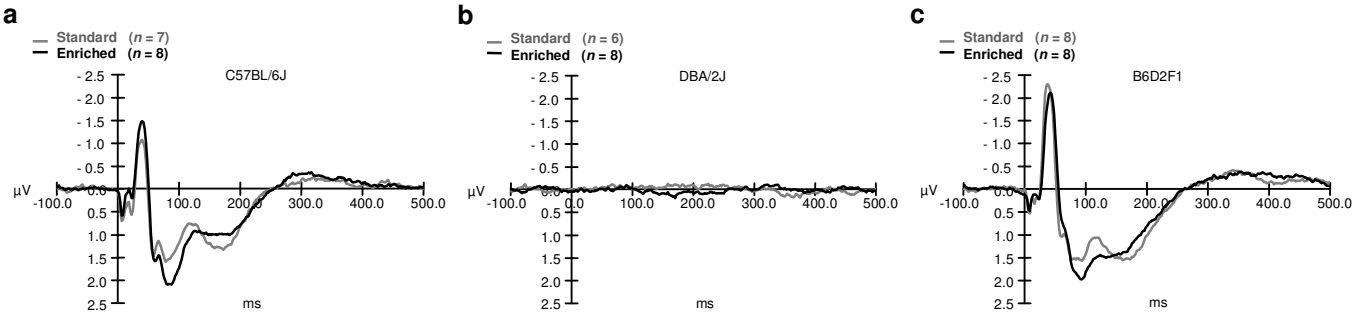

Figure 7 | Auditory evoked potentials. The record was done from the surface of primary auditory cortex in Standard and Enriched C57BL/6J, DBA/2J and B6D2F1 mice. These mice were never trained in Go/NoGo sound discrimination paradigm. This is a grand-average of four paradigms, wherein the stimuli had 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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Supplementary Information for

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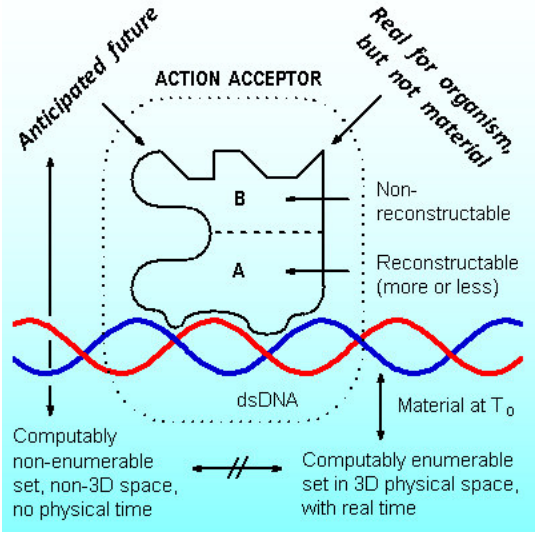
Evolution, ontogenesis and behaviour of organisms cannot exist without their own anticipated future. However the anticipated future is not material at the particular time T_0, it cannot be investigated by means of physics, chemistry and molecular biology, but it is real for given organism. The anticipated future interacts with material reality through an action acceptor. An evolutionary early action acceptor – the site of dsDNA that can bind potentially useful component – obviously has its own material part (dsDNA). Some other part of this action acceptor – *i.e.* some part (A) of the acceptable protein (an example of useful component) can be reconstructed on the basis of dsDNA with some success. However another part (B) of the anticipated component cannot be reconstructed on the basis of information, existing inside this physical system. Simultaneously, the part B is even more important for given organism than part A.

All above-mentioned components, namely dsDNA, part A and part B of the anticipated protein, are parts of the action acceptor (**Supplementary Fig. 1**). In this example, at given time point T_0, only dsDNA is material, whereas the anticipated parts A and B are not material ("not material yet"). Action acceptor provides interaction between space of vulgar materialism (or 3D physical space) and ideation space (or space of religious idealism).

Evolution, ontogenesis and behaviour of organisms are driven by interaction of ideation space with space of vulgar materialism. Ideation space contains anticipated future and remembered past, but it will be an error to assume that it is just a projection of known 3D physical space into the future or into the past. All properties of ideation space are significantly different, at least in their mathematical meaning, from the known 3D space. The entities in the 3D physical space comprise computably enumerable set (they can be unambiguously numbered 1, 2, 3, *etc*., at least theoretically), and they exist in real time: some time scale can be established (these entities can be organized in accordance with the above-mentioned time-scale more or less unambiguously, once again – at least theoretically). The entities in the ideation space comprise computably non-enumerable set (they cannot be numbered and each entity can contain in itself unknown number of identical or slightly different entities; this feature is not related to any problem with "infinity" – it is unclear where there are 1, 2 or 3 entities in one imaginary entity). The number of dimensions of ideation space (whether it is 3D, 2D, 1D, 4D or something else) cannot be specified also, because dimensions of ideation space comprise computably non-enumerable set as well. The time scale, or physical time, does not exist in the ideation space, and everything is looking so as everything is given "simultaneously" (but it is not "really simultaneously" – just the global time scale cannot be introduced, whereas local time-scales sometimes can be introduced (for example, during solving of some school problem in the field of classical mechanics), but they are not universal in any respect and they do not have any deep meaning or value).



Supplementary Fig. 1 | Evolution, ontogenesis and behaviour of organisms cannot be understood without their own anticipated future. However the anticipated future is not material at T_0 – it cannot be investigated by means of physics, chemistry and molecular biology. Any action acceptor provides interaction of physical space with ideation one.

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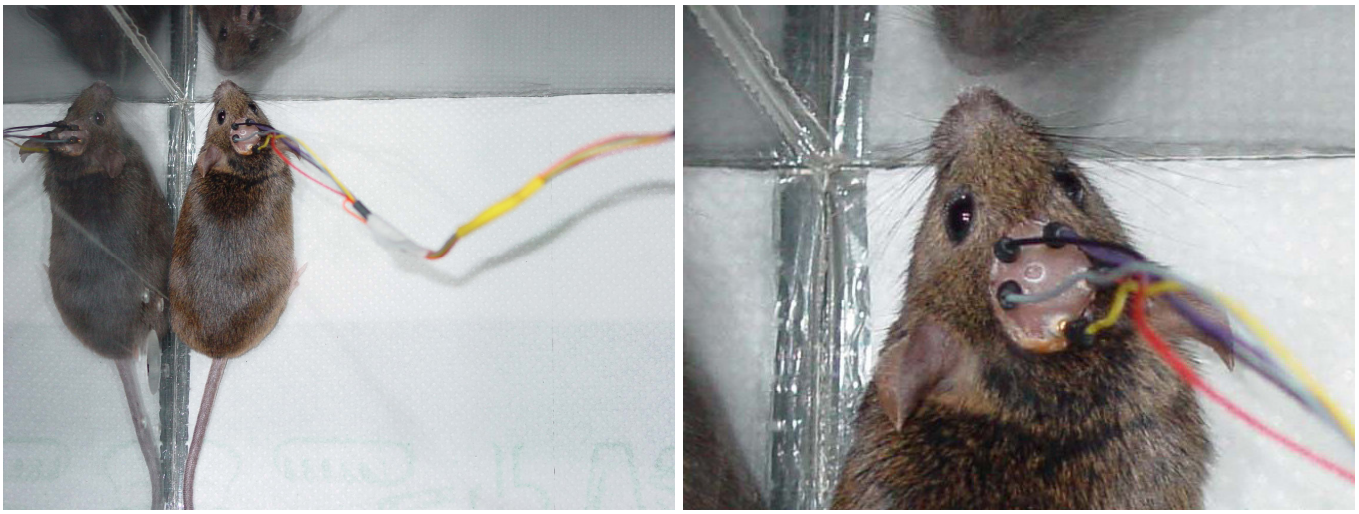


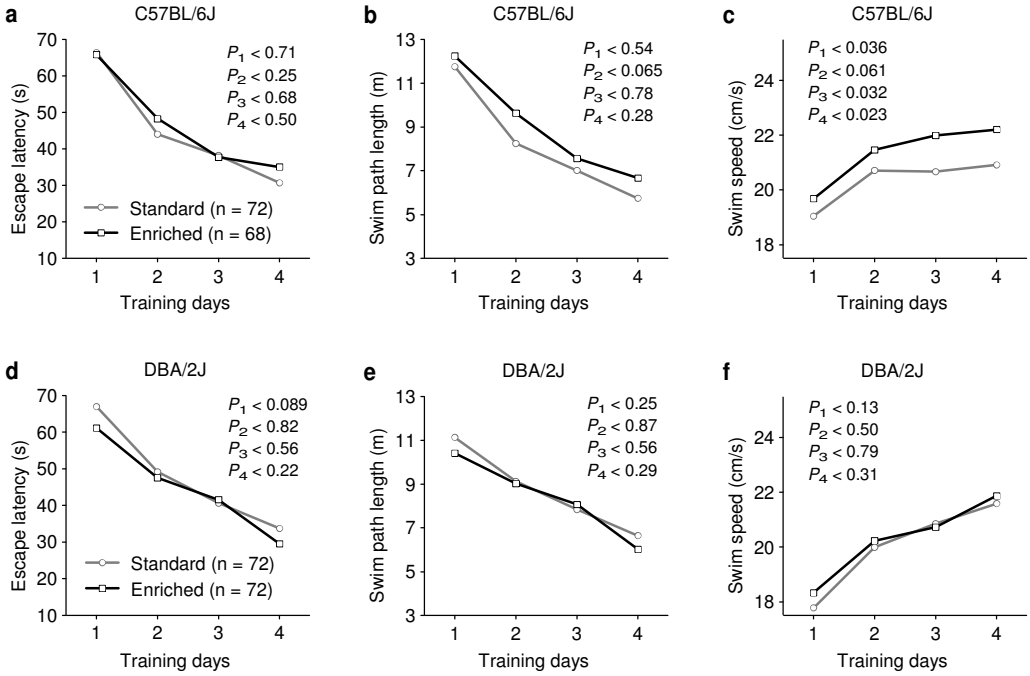
Supplementary Fig. 2 | Mouse, prepared for auditory event-related potential (ERP) recording, in the experimental chamber, genetic background 129sv. During surgery the animal was anesthetized with ketamine-xylazine (87 mg/kg ketamine + 13 mg/kg xylazine, i.p.). Electrode type is shown in the US Patent 8160688, Fig. 11(E). Blue – Reference; Black – First ground; Yellow – Second ground; Red – Right auditory cortex (-2.7; +3.5 mm from Bregma); Grey – Left auditory cortex (-2.7; -3.5 mm from Bregma). For all recordings shown in our article the recording electrode was placed 2.7 mm posterior to bregma, 3.5 mm to the right of the midline, reference – on the same hemisphere towards the right olfactory bulb. EEG was recorded in the dark.

The fact that the entities of ideation space comprise computably non-enumerable set has several very important consequences. First, many-many known mathematical statements and theorems are applicable only to computably enumerable sets and they are not valid with respect to computably non-enumerable sets (for example, among the most famous: the first and the second Gödel's incompleteness theorems – they are true only for computably enumerable sets)[14-15]. Second, contradictions can be solved in computably non-enumerable sets, contradictions can be resolved, *i.e.* some of contradictions can have several or many solutions. It is possible because some entities can contain other entities in themselves (the entities cannot be numbered in advance in a computably non-enumerable set). An important example is provided by the Theory of Inventive Problem Solving (TRIZ), developed by Genrich S. Altshuller[16-19], namely by the Algorithm of Inventive Problem Solving (ARIZ)[20]. The Algorithm of Inventive Problem Solving is an algorithm exclusively for humans, it is not for computers, and it cannot be called "an algorithm" in terms of contemporary applied mathematics. ARIZ is a set of instruction or a "tool" for humans for improvement of any given technical system. Contradictions in development of technical system can be solved in the frame of ARIZ by a well-prepared human. It is interesting to note that any technical system, as an object in physical space, is comprised of a computably-enumerable set of components. This statement is true for both old and new technical systems.

However the transition from one to another one is going into ideation space wherein components of technical system are not computably enumerable (at least those components that are important for solution of given contradiction in evolution of discussed technical system). Technical examples are provided in the books of G.S. Altshuller. For our discussion it is important that humans can work in the ideation space with computably non-enumerable sets and the results of this work can be materialized in the technical systems that exist in 3D physical space in full agreement with vulgar materialism.

Humans are not the only known creatures that can handle ideation space or can interact with ideation space. Any living organism that has at least one action acceptor (Peter K. Anokhin, 1955[10], 1974[11]) already has its own anticipated future and, thus, it has an interaction with ideation space (ideation space is real, but not material, as it is already known for us, and we can always add: "anticipated future is not material, but it is real for given organism – it is the main determinant of its behaviour). Even viruses have sites for binding of anticipated components in their

Supplementary Fig. 3 | Mouse C57BL/6J in the hole-board test (visual-tactile discrimination). This is a 6-min session of day 3, whereas during previous two days this mouse was tested on a classic 16-hole hole-board. During behavioural testing the light intensity was 25 lx in the middle of this arena (*i.e.* really dark, not like in this photo). The olfactory discrimination was done on the following days 4 and 5: the classic hole-board with round holes was used, but under one half of the floor the Mint odour was added: under each of 8 holes a portion consisted of 1.4 g of dried powder of Mint (*Mentha piperita*, that is hybrid [*M. aquatica* × *M. spicata*]) was placed.



Supplementary Fig. 4 | Morris water maze. Inbred C57BL/6J and DBA/2J female mice after standard (grey) and enriched (black) living conditions, mean values of each training day separately. Similar values for hybrid B6D2F1 mice (n = 68 [Standard], 75 [Enriched]) are shown in the **Fig. 4d-f**. Note that the enrichment effect (and very slight) can be seen only in the C57BL/6J mice and only as a minor increase in their swim speed (**c**). Simultaneously, B6D2F1 hybrids have shown dramatic improvement with high statistical significance in both escape latency and swim speed as a result of the same enrichment of their living conditions during their adolescence period. The enrichment is more effective for hybrids than for inbred mouse strains.

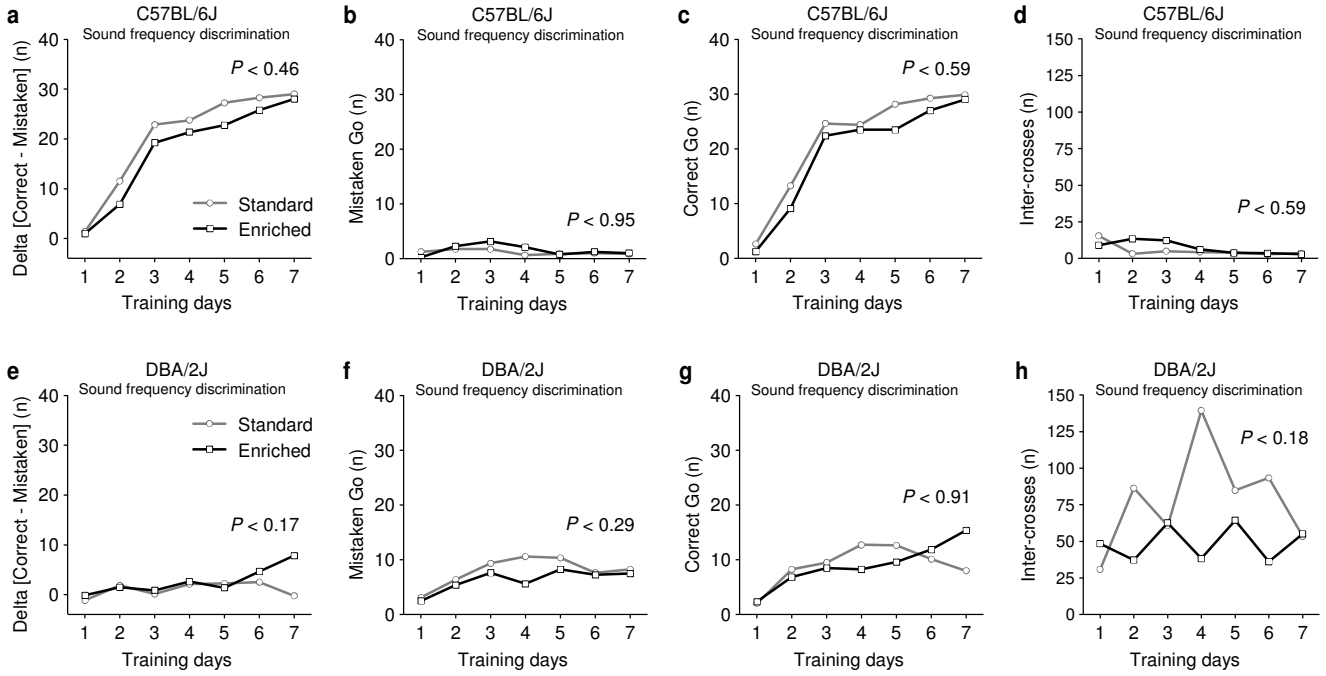
DNA (or in RNA – indirectly) and, thus, they are also leaving creatures with their own anticipated future. Consciousness is just an interaction between ideation space and space of vulgar materialism (interaction of "anticipated future and remembered past" with "neurons and neuronal groups in the brain"). Consciousness is nothing more and nothing else. And in these terms even the simplest living organisms (those are not dead at the moment of discussion) have consciousness (an interaction of ideation space with 3D physical space of their bodies).

With respect to humans it is not a secret that the results of human life are determined by human purposive behaviour. Many other known inputs, like talent, economical factors, external environment, education, are important, but deeply secondary with respect to human purposive behaviour. The future of a human is determined not by his or her education or by economical factors, but mainly by his or her anticipated future (and it is not a joke).

The same stands true for animals (and other creatures), for their evolution (an internally purposive process, driven by action acceptors), for their ontogenesis (also an internally purposive process, driven by action acceptors) and for their behaviour during short behavioural episodes (behaviour is driven by action acceptors also). With respect to evolution it is incorrect to assume that the effect of action acceptors resembles an effect of artificial selection, because if there are at least two action acceptors, acting simultaneously, it is not an artificial selection, but a creation of an object from at least two parts.

During early evolution, wherein co-variant reduplication was impossible, wherein DNA-polymerase and RNA-polymerase were absent, action acceptors were collecting and holding potentially useful components, dispersed in the environment, in order to increase the probability of interaction with them. DNA replication was impossible in modern way and existing dsDNA was collecting more or less similar to it short pieces of DNA, holding them together. Short DNA pieces were available by chance and this situation is not possible today in modern biological world. It was very-very long period of evolution, wherein co-variant reduplication was impossible – everything was based on collection of items, available by chance. The pieces of dsDNA that were holding collectable items are called now "action acceptors" – they were the first action acceptors in the history of life. Short pieces of DNA were collected by relatively longer DNA by the same way as other components – nothing could be replicated by means of a template – the molecular machinery for this task was absent. The first machinery that has appeared later was not for replication, but for linking together of collected pieces and for elimination of errors, the errors that were disturbing the interaction between relatively long and relatively short pieces of DNA.

Thus, the machinery for DNA reparation has appeared in evolution much earlier than the machinery for DNA replication. We are speaking specifically about DNA and not RNA, because the function of RNA was always secondary and such thing as "RNA world" was never present (RNA is not stable enough to collect and hold other components during long periods of time – it cannot serve the function of an action acceptor, the function of RNA was always intermediate). I guess that it is absolutely clear that the molecular machinery for DNA replication has evolved from the molecular machinery of DNA reparation, but not *vice versa*.

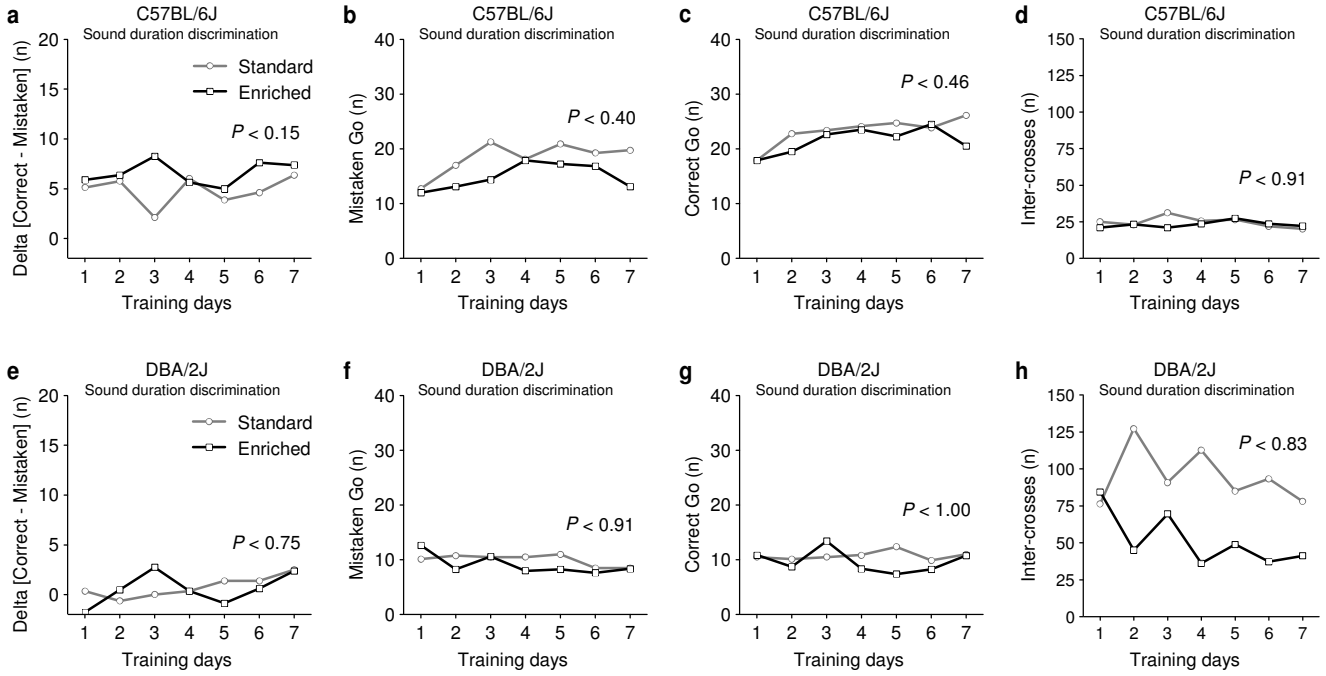


Supplementary Fig. 5 | Go/NoGo sound frequency discrimination task. Contrary to B6D2F1 hybrid mice (**Fig. 5**), which have shown the improved sound frequency discrimination ($P < 0.027$, **Fig. 5e**), the decreased number of mistaken "go" ($P < 0.023$, **Fig. 5g**) and the decreased dumber of inter-crosses ($P < 0.0023$, **Fig. 5h**), no such effects of enrichment were observed in the inbred mouse strains C57BL/6J and DBA/2J. "Inter-crosses" are events when an animal is moving from one compartment to the opposite one between series of signals (neither "Go" nor "NoGo" signals are given). Such movements are not punished and an animal can demonstrate here absolutely free behavior without any negative or positive reinforcement.

The interaction between ideation space and 3D physical space (or, in other words, the interaction between space of religious idealism and space of vulgar materialism) was always a driven force for evolution – from the early stages of evolution before covariant reduplication till modern neuroevolution, and including neuroevolution in humans. In accordance with Henri Bergson (1907)[21], ideation space is real – it is real, but not material, it is reality. And entities in this space are not "invented" by humans, but could be "discovered" by humans (like mathematical regularities) – that is religious idealism. Mikhail M. Bakhtin[22-23] has mentioned that "metaphysics is always religious", but we are talking here not about physics or metaphysics, but about living organisms those do have their own anticipated future (not about physics). In accordance with Ludwig Büchner[24], if there is such entity as "ideation space", it is solely invented by humans and cannot have any interaction with material world. That is why ideation space is not interesting for natural sciences (even if such entities as "soul" and "spirit" could be discussed by humans – they have no interaction with reality) – that is vulgar materialism. In modern science "vulgar materialism" is re-branded into "realism" (keeping in mind that there is no other reality than material). Karl Popper[25-27] serves as a good example of a "naïve realist" who in fact should be named a "vulgar materialist". This is true for the vast majority of researchers today. Even in humanitarian sciences, with an important exception of Bakhtin, modern researchers are trying to copy-paste thought style from natural sciences in order to be "more scientific". In its turn, in natural sciences the researchers are trying to copy-paste thought-style from physics, assuming that it is a good idea or in order to be looking "more scientific" as well. Humanitarian sciences, in accordance with Bakhtin, are sciences about soul and spirit, but not exclusively about material artefacts through which the soul and spirit could be accessed (sometimes).

Action acceptor does provide interaction between ideation space and 3D physical space. Such interaction does exist in nature. In the frame of vulgar materialism and in the frame of contemporary science, the term "nature" is used exclusively as an equivalent of "material nature", because no other "nature" is known for modern sciences, except material one. But for as, as well as for Bergson and for all other living organisms, in fact, the ideation space is the most important part of living nature.

The difference in properties of ideation space and 3D physical space makes impossible any direct projection of one into another. Namely, computably non-enumerable set without time scale in the ideation space and computably enumerable set with real time in 3D physical space cannot be projected one into another unambiguously. It is mathematically impossible to project computably non-enumerable set into computably enumerable one. That is why the discussion of 1850-1900 about psycho-physiological parallelism has clear solution: psycho-physiological parallelism is mathematically impossible. We cannot take hypothesis of psycho-physiological parallelism even as a temporal or partially true solution, even for the sake of simplicity, because it is deeply erroneous and it is based on presupposition that is known to be false. And it does not matter that this topic about psycho-physiological parallelism was "hot" 150 years ago: there is no physical time in the ideation space and all events are given simultaneously, they do co-exist simultaneously in the ideation space. That is why the thoughts from 3000 years ago, as well as the insights from 150 years ago,



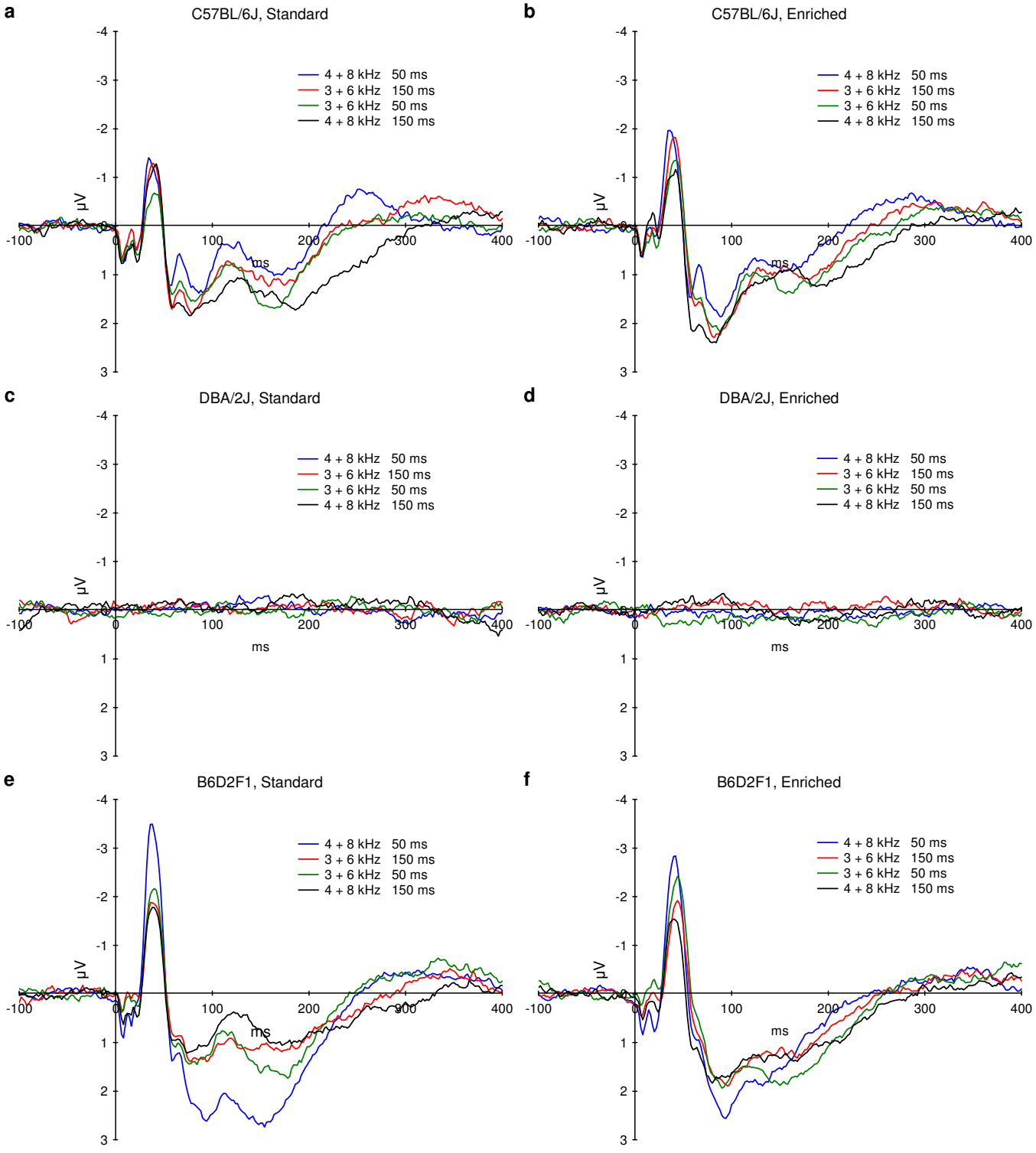
Supplementary Fig. 6 | Go/NoGo sound duration discrimination task. Sound **duration** discrimination task is much more difficult for mice than sound **frequency** discrimination task, but it is exactly in this task the adolescent enrichment provides opportunity for hybrid mice to outperform all other mice with highest statistical significance (**Fig. 6a**). For hybrids: improved sound duration discrimination ($P < 0.0011$. **Fig. 6e**), decreased number of mistaken "go" ($P < 0.030$, **Fig. 6f**), decreased number of inter-crosses ($P < 0.0063$, **Fig. 6h**). Note that in the Morris water maze (**Fig. 4f**) the same animals have shown increased swim speed (more movements), but in all Go/NoGo tasks they always demonstrate less inter-crosses (less spontaneous movements).

may have more deep impact on our thought-style than events of today.

If the hypothesis of psycho-physiological parallelism is false, then, where is memory, where is the memory "stored"? And what is in the brain? Memory is in the ideation space that is not material. Brain contains only cells and groups of cells that were pre-selected from the pre-existing repertoire to serve as a symbolic reminder. "Symbolic" – because when we are looking, for example, at a fire, we do not have plasma in our brains. That is why the reminder is always symbolic. Sometimes humans have a tendency to mix up the entity with its reminder (for the sake of simplicity, of course). For example, when we are looking at a sheet music with notes, we do not have music in our hand, we have only a reminder about music. This is especially obvious if we compare real live sound of such instruments as cello, violin or clarinet (with an ultra-soft reed) being played by humans with corresponding sheet music. It is not even funny to discuss a "percent" of real sound that is reflected in the sheet music – it could be different even for the same piece and the same player in different time. Each note has its "beginning", its "flow" and its "end", and each of these three parts can be played differently (for example: *pp* – *mf* – *pp*), whereas in the corresponding sheet music we have one note with its duration. We are speaking about music, when it is playing by humans, not by students. Students are usually forced to perform (not to "play", but to "perform") exactly as "it is written", and they are performing as well as they could, with a few semi-random mistakes on the top of this (students, contrary to humans, are not trying to play with the most beautiful sound, but they are trying to avoid mistakes as much as possible) – there is nothing interesting here and nothing to discuss, unfortunately. This is not a humans' thought-style, but it is a students' thought-style that cannot be changed or modified.

Thus, the brain contains only reminders – they are completely physical entities with full agreement with vulgar materialism. The cells and group of cells, those have comprised a reminder, were selected from the pre-existing repertoire of cells and groups of cells by the requirement from the ideation space. A reminder or a set of reminders in the physical space of brain can be significantly less complex (much more simple) than a corresponding entity in the ideation space. That is why a relatively simple brain can solve relatively complex tasks. The tasks are being solved not exclusively in the space of vulgar materialism, but by means of interaction of ideation space with space of vulgar materialism. And the ideation space has no limitations in complexity. We all know that human brain is a very-very complex entity. However the corresponding ideation space could be much more complex than human brain! And it is more complex not only extensively, but it can have more dimensions than 3D space, it may contain computably non-enumerable sets and the quantity of dimensions could be computably non-enumerable also – the all mentioned above provides indisputable fluidity, unimaginable for strictly material 3D physical space of vulgar materialism.

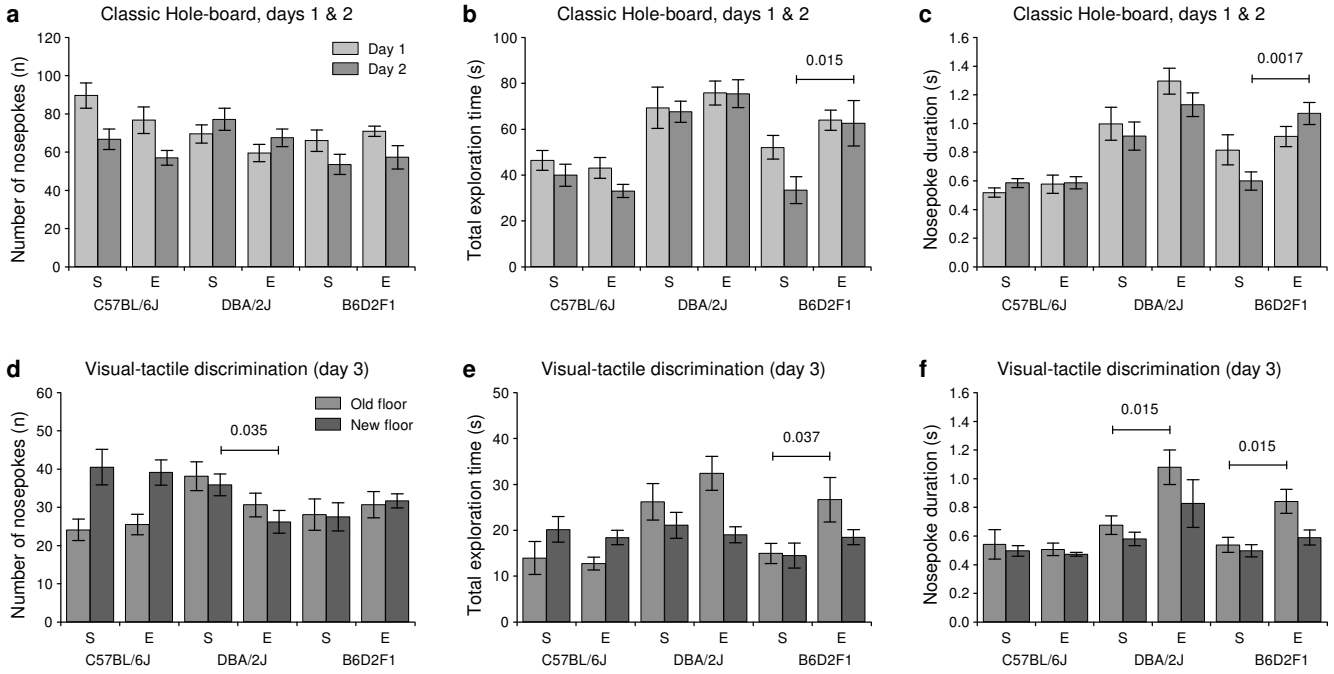
Religious idealism does not reject physical 3D world as a material entity, but it rejects vulgar materialism as a thought-style. It is like a new system of coordinates with additional dimensions – in view of this system of coordinates everything



Supplementary Fig. 7 | Auditory evoked potentials. Four paradigms, wherein the stimuli (2700 per paradigm) 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 observed non-significant similar alterations in P2 (50 - 200 ms) in the C57BL/6J and B6D2F1 could be explained not only by an alteration in auditory signal processing, but by a slight spatial shift of functional fields in the brain with respect to scull (individual variability in morphology), whereas the electrode position was always the same with respect to Bregma. Note also: in such electrophysiological recordings a lot of variability arises as a result of unavoidable variability in surgery.

could be re-considered: individual behaviour, ontogenesis, evolution, understanding of music and culture in general.

How can we imagine that ideation space requirements or requirements form ideation space can select something in



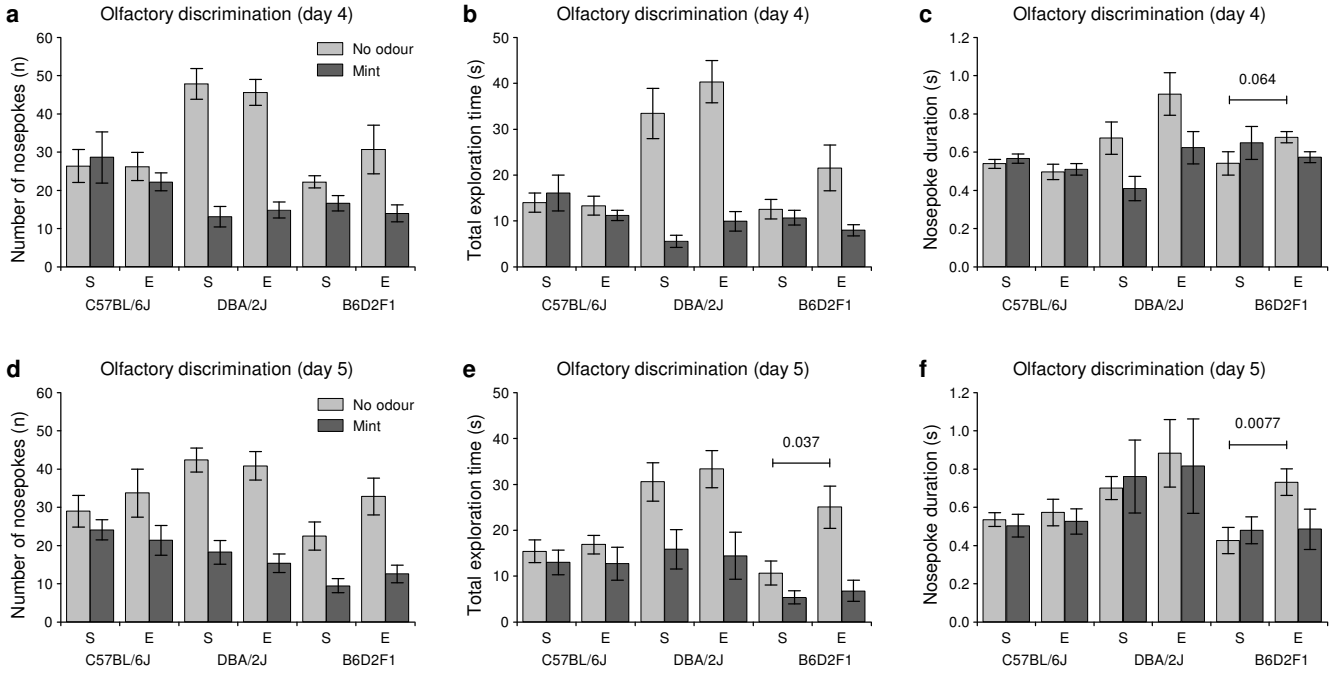
Supplementary Fig. 8 | Classic Hole-board and Visual-tactile discrimination. (**a-c**) Classic Hole-board, days 1 and 2 (6 min daily; 16 holes d = 25 mm, arena 40 × 40 cm). (**d-f**) Visual-tactile discrimination (see photo in the **Supplementary Fig. 3**). (**a**, **d**) Number of nosepokes. (**b**, **e**) Total exploration time. (**c**, **f**) Averaged nose-poke duration. S – standard, E – enriched. Note the absence of enrichment effect in the number of nosepokes (**a**), and remarkable increase of nosepoke duration in the enriched B6D2F1 mice during the second day (**c**). Note the absence of enrichment effect in the exploration of new floor (**e-f**), but significant increase in nosepoke duration in the old floor in the enriched DBA/2J and B6D2F1 (**f**). Mann-Whitney U-test. Mean ± SE.

material world? We all know that sound quality of any musical instrument is important. Let's discuss clarinet, because it contains material parts, convenient for discussion. What is determining the sound quality of a clarinet? Any vulgar materialist will say that the sound quality depends on reed, mouthpiece, barrel, ligature, clarinet itself, its bore diameter, a lot of other parameters, including internal geometry of mouthpiece, its material, internal geometry of barrel and its material, and also the experience of player will not be forgotten by a vulgar materialist, because it is also something "objective". And many-many other things like material of clarinet and its quality, quality of production, are important also. All physical factors are important here. All the above-mentioned could be false, or it could be absolutely correct, but it is of minor importance, because the most important factor is completely forgotten here.

The sound of a clarinet is determined by… the anticipated sound! Yes, because it is a human who is playing clarinet. The reed, the mouthpiece, the barrel and even the clarinet itself are selected by a human in order to have anticipated sound. It is also a human who produces the best possible sound from any randomly chosen mouthpiece. In order to do this, at least 5+ years of daily experience is required for a large-bore clarinet, and for a narrow-bore clarinet an additional 2+ years of daily experience specifically with a narrow-bore clarinet is required. We are speaking here about humans, not about students. Students are playing everything "as is" with always mediocre (a soft term) sound. Some more technical remarks: we are keeping in mind an ultra-soft reed only, because we are expecting clear and "live" sound without disturbing artefacts from *pp* to *mf* and back (up to *ff* in clarion register). An example of ultra-soft reed is: "Vandoren Traditional #1.0", and usually "significantly used", *i.e.* not new. Clarinet, mouthpiece and barrel should be in full resonance through out the range; otherwise the reed will not be flying, supported by air pressure. A narrow-bore clarinet produces smaller pressure and it requires even softer reed and higher experience level in order to have clear and "live" sound.

Of course, any clarinet in such set-up is not a self-playing instrument, like cheap electronic piano, wherein sound quality is pre-programmed on the factory; it requires significant experience (several years) even in order to play very simple (and slow) pieces, like in "*The Klezmer Wedding Book*" of Giora Feidman (1993)[28]. Giora Feidman, Moshe (Moussa) Berlin, Chilik Frank and, in fact, many-many others are playing clarinet beautifully, and there are clarinet records made before 1936 in the Eastern Europe with amazing ("live") sound. Why American students are playing clarinet the way they are playing it? G-d knows… It is even more disappointing that, due to the capitalistic driven forces in clarinet mass production, even "professional clarinets" are optimized for very-very advanced students, but not for humans.

The capitalistic competition was, and it remains, the most important driving force of technical revolution and technical progress. And it was recognized many-many years ago (before the appearance of Darwinism, *i.e.* before 1865)[29-30] – Pierre-Joseph Proudhon has described it in his book "*The Philosophy of Poverty*" (1847)[31], whereas Karl Marx in his work (also 1847)[32] "The Poverty of Philosophy. Answer to the *Philosophy of Poverty* by Mr. Proudhon" was trying to criticize Proudhon, but



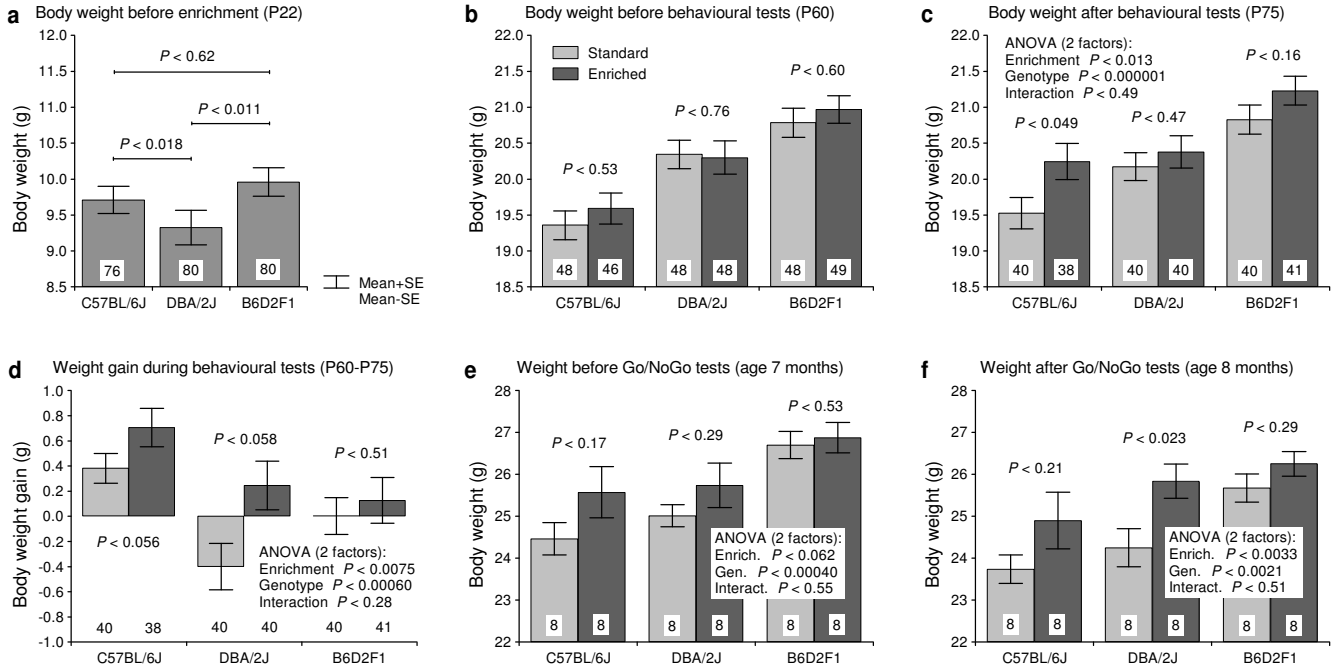
Supplementary Fig. 9 | Olfactory discrimination in the Hole-board task. (**a-c**) Day 4 of the hole-board test and it is the first day of odour presentation. (**d-f**) Day 5 – replication of day 4. Under 1/2 of the floor the Mint odour was placed (see **Fig. 3** legend). Note strong avoidance of Mint odour in all DBA/2J and absolute absence of discrimination in all C57BL/6J. Once again, the enrichment effect was observed in the hybrid mice, as increased nosepoke duration in standard holes without odour (**c**, **f**). Note that the enriched hybrids had also longer nosepokes during the second day of classic hole-board (**Supplementary Fig. 8c**) and longer nosepokes in standard holes during visual-tactile discrimination (**Supplementary Fig. 8f**).

Marx was unable to invent any equivalent mechanism for a non-capitalistic society that can promote technical progress. And we all know now from the real history of socialistic society (USSR) that technical progress can exist in such society only due to external pressure, or external competition, either in the form of war or "cold war" (look at the history of space flights). In addition, in a non-capitalistic (socialistic) society not only any technical progress is practically absent, but the quality of goods is very poor and there is no mechanism for its improvement (both factors entail very low production culture – and it is not a speculation, but a part of real history). All technical evolution in socialistic countries was based on ideas, borrowed from capitalistic society, the ideas that was borne and developed in capitalistic competition.

However in the case of clarinet the capitalistic competition has led towards optimization with respect to absolutely erroneous "ideal final result". Fortunately, the violin and the cello have avoided the above-mention terrible degradation (only because they do not have the material parts that could be optimized towards erroneous goal, could not be optimized for somebody who is lazy and inexperienced). However, the clarinet has served us as a good example for illustration how the ideation space determines some elements in the purely material world.

Why would we like to listen to "live" sound, but not to "reproducible" of even to "pre-programmed" one? There is a controversial distinction of humanitarian sciences between the soul and the sprit. Spirit fully belongs to a given human being (all his driven forces, his efforts, everything is included into the spirit, but it disappears together with human's death). The soul of a given human exists only in the consciousnesses of other living beings (typically – humans), or in the consciousness, al least, of one another human. The soul is always some kind of understanding or reflection of a given human by another living creature. At the moment of human death nothing goes on with his soul, because it exists not in connection with his body, but in the consciousness of another one. This distinction between the soul and the spirit is controversial, because the traditional religious thought-style does not use is (at least – explicitly). For traditional religious thought-style the soul and the spirit comprise one unitary entity. When we are listening music, or when we are playing a musical instrument ourselves, we are listening to a soul of another individual. Or we can say that the person who is playing music is like an author, who is listening to a soul of a hero (there is a term "character", but we would like to say "hero"). When we are looking at a dancing pair (male and female humans) there is always a strong tendency to say that they are dancing themselves and, thus, to extrapolate the essence of this dance into internal worlds of these two individuals. However, in fact, we see only two dancing heroes of this dance and the souls of these heroes have nothing common with the spirits of dancing male and female. The dancing person expresses not his own spirit, but the soul of the dancing hero of this dance. The same with music: when we are playing a musical instrument, we are expressing not our spirit, but we are listening to a soul of another individual. That is only why the sound should be "live".

And any live sound in a clarinet requires an ultra-soft reed. That is how the ideation space determines the properties of material world. We are omitting here such technicalities that it is



Supplementary Fig. 10 | Body weight before and after behavioural tests. (**a**) Body weight of inbred C57BL/6J, DBA/2J and hybrid B6D2F1 female mice before cage enrichment. (**b**) Weight immediately after enrichment, before behavioural tests. (**c**) Weight after behavioural tests: O-maze, Open-field, Object exploration and Morris water maze. (**d**) Weight gain during mentioned above tests. (**e**) Weight at the age of 7 months, before Go/NoGo tests. (**f**) Weight after Go/NoGo sound frequency discrimination and sound duration discrimination tasks. Body weight is always discussed as the most impressive indicator of hybrid vigour. Here we see it in the F_1 hybrids as well. Cage enrichment facilitates weight gain only (**c**-**f**). Mann-Whitney U-test. Mean ± SE.

impossible to play ultra-soft reed with "frozen lips" or "well-developed embouchure" (even along duration of a single note the lips' position and the air flow at the beginning, in the middle and at the end are not the same, and they could not be the same if we are going from *pp* to *mf* and back to *pp*, for example). Good kinesthetic memory is required here. There is more general scientific term "procedural memory", but it is not enough precise. "Kinesthetic memory", how it is understood in the neuro-linguistic programming (NLP)[33-37], is exactly what is required.

Neuro-linguistic programming is considered as a non-scientific branch of activity today. Everything that is dealing with anticipated future of humans or any other living beings is considered today as a non-scientific or anti-scientific activity. Everything that is not material is not real for contemporary science. And the science itself has evolved into such an object of idolatry (look at the usage of the term "scientific" as an equivalent of the "good" and the opposite term "non-scientific " as an equivalent of the "bad") that the Second Commandment must be directly applied to such entity. It is a double shame to keep such a teaching that is based on vulgar materialism as an object of idolatry. We can say that natural sciences are sciences about material world "in accordance with their definition". However as soon as it is discovered that behaviour, ontogenesis and evolution of living beings are determined by ideation space, by their anticipated future, and by interaction of ideation space with material world, natural sciences cannot be compressed in to the main frame of vulgar materialism anymore (or, at least, they cannot be compressed in an isolated form).

To see the difference in thought-styles we can look at the interpretation of a "mysterious event" by the vulgar materialism and religious idealism. "Mysterious event", in accordance with vulgar materialism, is an event that is in contradiction with known laws of physics, chemistry and molecular biology. Of course, real mysterious event, as all the mysterious taken together, is impossible in the frame of vulgar materialism. In accordance with religious idealism a mysterious event is driven by an input from the ideation space and its contradiction with known or even unknown laws of physics, chemistry and molecular biology is not required.

It is important to know that ideation space and space of vulgar materialism can interact, but they do not intermix. The interaction is important. Many-many ears ago humans did an important invention when they have learned how to go in a sea against wind under sail. It was possible to do only being on a surface between the two media – air and water. Only the interaction with both of them simultaneously provided the possibility of movement in the desired direction, even if it was against wind (nobody says that it was easy, but it was possible). If, instead of two separate substances (water and air), we would have their intermixture like in a foam – any purposive movement would be impossible. Specifically, it would be possible to move only together with all this foam or to use exclusively ones own force to move inside it. It is just a metaphor, but it is trying to explain our more complex case, wherein an action acceptor, being on the border between 3D physical space and ideation space (that is not 3D), provides possibility to evolve (an individual behaviour, ontogenesis and evolution – just three

examples of interaction of ideation space with 3D physical space by means of an action acceptor).

The religions those are based on idolatry allow some kind of admixture of ideation space with material one. As a consequence, they implicitly require the existence of the same type of miracle that was discussed by vulgar materialism as "impossible". There for there is a tendency in the frame of such religions to focus attention upon those natural events that could not be explained by the contemporary science. They see here the presence of G-d. For example, look at the logic of "Intelligent Design" with its "irreducible complexity" (a Christian teaching) and the evolutionary views of contemporary science (Darwinism with all its modifications). Evolution cannot be explained by natural selection, because the "irreducible complexity" was formed by action acceptors. However evolution cannot be explained by direct and material involvement of G-d as well.

For those religions that are not based on idolatry, we can say that there are no physical time in the ideation space and solely for this reason it is not so important whether the living world was created in six "days" or six "periods", but it is more important that it was created by purpose (*i.e.*: purposively). And not only purposively, but the result of each step was assessed and approved as being good, as it is described in *Genesis* (The First Book of Moses)[38]. There is a secret: G-d is real. However there is no need to seek or to search for Him as it was proposed by vulgar materialism (in the 3D physical space, of course). Ideation space is real, but it is not material. It was not "invented", but it was "discovered" by humans (as well as mathematical regularities, for example). And evolution of living organisms proceeds by means of interaction of ideation space with material 3D physical space. Evolution is directed by G-d in person and there are no analytical means that can show the opposite.

Let's return to clarinet technicalities. There is a notion that if the reed is an ultra-soft (Vandoren Traditional #1.0), it is impossible to have "classical sound". This statement is false. I have "classical" or "concert" clarinet set-up that has classical sound with an ultra-soft reed: mouthpiece "Denman 3+" (glass mouthpiece with greenish glass and several small air bubbles inside; John Denman was a classical clarinettist, generally underrated in my opinion). The most important in any mouthpiece is its internal geometry and it cannot be transmitted in simple numbers, nevertheless for an external impression: its length from the barrel to the highest point of its opening is L = 69.0 mm, the length of its opening is l = 31.25 mm. For comparison, Vandoren B45 has L = 72.5 mm and l = 31.5 mm. All measurements are taken alongside the table surface. It has narrow metal ligature with single screw that was cut from standard student ligature. Many players those prefer glass mouthpieces are using the same narrow metal ligature: Chilik Frank, Moshe (Moussa) Berlin and many others. Barrel was taken from some pre-war Selmer large-bore clarinet (I never saw this instrument, the name is unknown, but its internal surface is polished up to indisputable quality). And the instrument itself is G. Pruefer pre-war large-bore clarinet with articulated C#/G#, serial number 4987, the production year remains unknown.

These is also an opinion that in order to play with nice sound someone should have mouthpiece like "Kaspar-Cicero" from the "golden era of clarinet" or mouthpiece like Giora Feidman has in order to play Klezmer. That's all wrong. The mouthpiece should be in full resonance with given barrel-clarinet combination (with respect to chosen reed, of course). The rest is less important. I have a no-name plastic mouthpiece without any marks or numbers (black plastic, covered by a thin layer of some other black plastic, probably with better mechanical properties; length L = 70 mm, opening l = 34 mm). *I.e.* it is rather short mouthpiece with very long opening (in comparison with Vandoren M13, for example, which has L = 72.5 mm and l = 32.5 mm), with original facing (non-refaced) – and it plays in resonance with clarinet "E.J. Albert, Brussels, SOLE AGENTS J. HEYWORTH & SON, BLACKPOOL – PARIS, LONDON" in a semi-klezmer style. This it is a pre-war large-bore clarinet, it has no serial number, but it has top-level quality. Despite it is manufactured by E.J. Albert, it has French/Boehm fingering system, without articulated C#/G#. The original barrel should be pulled several millimetres up in order to be in tune. Rovner ligature (old Rovner C-1R, that was manufactured before the introduction of distinction between the "Dark", the "Light" and "Mark-III"; it is like "Mark-III", but without metal labels on the left and right sides, those are obviously useless) works well with this set-up.

There is also an idea that in order to play with clear and "rich" sound someone should have a large-bore clarinet. Unfortunately, this statement is partially true – at least it seems correct with respect to clarinets with French/Boehm fingering system. However for Albert clarinets (two lover rings, two upper rings, two left rollers and two right rollers) it is possible to have a narrow-bore clarinet with perfect sound. I have a key "C" clarinet (contrary to more common Bb) with very narrow bore and Albert-fingering: "V. Kohlert SOHNE, GRASLITZ, CZECHO-SLOVAKIA", serial number 252949, and I believe it was manufactured in 1925). It was a cheap "simple" clarinet at the moment of its production; it has not the best alloy for mechanics (not a "German silver"), its axles are manufactured using rather soft steel. Key "C" mouthpieces are very limited in their availability, and in order to use Bb mouthpiece with the key C clarinet the original 50 mm barrel should be replaced with 45 mm barrel (in fact, my barrel was taken from some old French clarinet and several millimetres of wood from the middle were thrown away to have 45 mm in total). Then, among mouthpieces for Bb clarinet, only mouthpieces for very-very narrow bore clarinet could be used. After the end of World War II it was a fashion for narrow-bore clarinets under mark "Artist Model". In short: mouthpiece "Artist Model, Penzel-Mueller, Long Island City, NY, 2*" (this is a post-war hard-rubber; very-very slightly refaced on its tip only – slightly more open than original "2*", L = 72.0 mm, l = 30.5 mm; the original Kohlert wooden mouthpiece for this key C clarinet had L = 67.0 mm and l = 30.5 mm, it is kept "for reference") did the trick with "LUYBEN (Made in USA, Pat. Pend.)" ligature (made form opaque polyethylene). Albert-system clarinet is supposed to be played using so-called "basic simple vent fingering", where possible. It is usually assumed that Albert-system clarinet is more difficult to play in some respect than French one. However, in fact, it is a student-level opinion, because humans remember each finger combination as a whole and not "finger-by-finger" – this entails absolutely the same level of complexity for Albert-system and Boehm-system clarinets. In is also interesting to note that humans who are playing Boehm AND Albert are playing Boehm with better sound than those who are playing Boehm only (this is only a statistical generalization, of course, with possible exceptions). Why it is so – nobody knows.

I have a narrow-bore Boehm clarinet, manufactured, I guess, in 1948: "G. Pruefer, Artist Model, MFR PROV. R.I., Carl Fischer Exclusive Distributor" with serial number 16801. Mouthpiece and barrel were selected to be in a more or less acceptable combination to be in tune and to provide resonance for ultra-soft reed: mouthpiece "Selmer Clarion HS*" (glass mouthpiece, No K201, CRYSTAL CLARINET HSX, sold by Norman Music, Ocala, Florida, for $21.50, many years ago; L = 69 mm, *l* = 31.5 mm), barrel from Selmer Signet (inversed-cone wooden narrow-bore barrel, which occurred to be more compatible with particular combination than original cylindrical-bore barrel with the same length 66 mm). The already mentioned LUYBEN ligature was working OK with this combination… However, despite it was playing "not bad", the sound quality was definitely mediocre in comparison with both large-bore G. Pruefer with articulated C#/G# and large-bore E.J. Albert (also Boehm/French-system). It is true that a negative example has not such a weight as a positive one (many unexpected things could be non-optimal), but it should be remembered for future [this speculation occurred to be correct: later it was shown that mouthpiece Vandoren M13 Lyre, described below, produces better result with this clarinet-barrel combination than the above-mentioned Selmer Clarion HS*]. Why it is practically impossible to achieve the same sound quality with narrow-bore Boehm clarinet as with narrow-bore Albert – also remains a mystery. The idea that "Kohlert with Albert fingering key C is shorter than G. Pruefer Artist Model key Bb" does not provide satisfactory explanation, because the Kohlert bore also has significantly smaller diameter than the Artist Model one. The truth is the following: 1) for a narrow-bore clarinet, in order to achieve the same sound quality, the reed should be even softer than the ultra-soft reed for a large-bore clarinet; 2) the requirement for resonance for a narrow-bore clarinet is tighter than for a large-bore one – the system with narrow bore should be in better resonance to be playable; 3) the required experience and the accuracy should be higher for a narrow-bore clarinet, in order to play it with the same or about the same sound quality as a large-bore clarinet (everything with ultra-soft reed, of course).

There is also one large-bore clarinet, manufactured relatively recently, about year 1970, by G. Pruefer, namely with labels "PRUEFER WOODWINDS, PROVIDENCE R.I., USA, **Silver Throat Deluxe**". I have an example with serial number 66729. Silver Throat Deluxe is a hard rubber clarinet, contrary to all wooden clarinets, discussed above, and it has a tube made from metal alloy inside the upper section. This tube is very thin in comparison with the surrounding hard rubber and it has nickel-silver colour. The mechanics of this clarinet is manufactured from aluminium alloy, covered/plated by shiny material/metal, and the pads are done from real leather and they have red colour. This instrument is interesting not only because it has rich and "live" sound with an ultra-soft reed, being paired with appropriate mouthpiece and wooden barrel (non-stock, of course, because original barrel is hard rubber), but because it can be bought, it can be acquired relatively easily, and it can be used either as a first step towards an ultra-soft reed or for outdoor performance (it is a hard rubber and it can be used in a rainy weather). Mouthpiece: "BRUNO Claude Lackey M" (it is an ivory plastic mouthpiece, it is a rather short mouthpiece with long opening, L = 70 mm, *l* = 34 mm; it is known to be producing "harsh" sound when it is paired with a narrow-bore clarinet, but Silver Throat Deluxe is a large-bore clarinet, and with Rovner Mark-III ligature and Vandoren Traditional #1.0 reed the sound is not "harsh"). Vandoren MPs cannot be used with Silver Throat Deluxe (they are for a narrow-bore clarinet).

It is interesting to note that "Bruno Claude Lackey M" in ivory plastic is looking like a copy of the mentioned above no-name black plastic mouthpiece, paired with E.J. Albert large-bore clarinet (similar internal geometry and external appearance, except the colour of plastic; L = 70 mm, *l* = 34 mm). They produce rather similar, but not identical, sound also. Barrel for **Silver Throat Deluxe**: wooden large-bore cylindrical barrel, rather short (I have a 60 mm barrel with a microphone pick-up), it should be pulled up several millimetres (about 5-6 mm) to be in tune. So, the final configuration is rather close to the above-mentioned E.J. Albert configuration: short barrel (63.5 mm – Albert stock), significantly pulled up (about 4.5 mm up). Obviously, not only the total barrel length, but the space between the barrel and the upper section, its volume, has an impact; but it works the best way exactly as described.

However, what if some external unavoidable force forces somebody to use "strength #3" reed with some "Vandoren" mouthpiece? And, on the top of these "requirements", the available clarinet is a randomly chosen instrument, usually with a narrow bore? Students are typically placed exactly into the above-mentioned situation… What to do? Take reed "Grand Concert Select Thick Blank 3" (it is manufactured by Rico, not Vandoren, and the box typically has, in addition to "Rico", "D'Addario" logo) – it has officially strength #3 (do NOT take any Vandoren #3 reed – and it is not a random remark here, it is not a joke). Take mouthpiece "Vandoren M13 Lyre, Series 13, Profile 88". Take ligature "Rovner Mark-III (MK III)". If this combination will be more or less compatible with available clarinet and barrel (and there is relatively high probability of not so bad compatibility with a narrow-bore clarinet, like with the above-mentioned "G. Pruefer Artist Model" clarinet (with "Selmer Signet" barrel), just because the set-up with strength #3 reed is less sensitive to full resonance requirement than any set-up with an ultra-soft reed), the sound could be not so bad. It will never be so beautiful, as with well-selected set-up with an ultra-soft reed and large-bore clarinet, but still not bad. Nevertheless even with a narrow-bore clarinet, like with the above-mentioned narrow-bore Pruefer Artist Model with Selmer Signet barrel and Vandoren M13 Lyre mouthpiece, if it is occurred to be in a good resonance, it would be better to take reed "Vandoren Traditional #1.0" and to play accurately (but this advice is not for a student).

What does "live sound" mean? We all know this, of course. However I would like to specify just for reference: listen to any record of Yossele Rosenblatt or any other cantor of equal rank. That's live sound.

These two pages of clarinet technicalities, rather controversial in their contents, show that humans select the material elements from the pre-existing repertoire looking for the anticipated sound quality. Klezmer and classical set-ups are different, because the anticipated sound is different: the classical sound is more canalized, whereas the Klezmer sound is more meta-stable and more "live". Nothing is in contradiction with the part of vulgar materialism: material elements determine sound quality. However the selection of these material elements is determined by the anticipated future, *i.e.* by religious idealism. The cells in human brain, those can serve as a reminder, are selected by the

anticipated future as well. Their spatial/morphological and biochemical properties are important, but only in view of their potential selection/collection to be used as a reminder. However it was the anticipated future (non-material entity) who has determined the fact of their selection/collection.

How do we know that entities in the ideation space comprise a computably non-enumerable set? This statement has status of an experimental observation (as well as, for example, the second law of thermodynamics – it was shown in 1991 by Albert-Victor I. Veinik (*The Thermodynamics of Real Processes*, 1991)[39] that all logical, theoretical and statistical proofs of the second law of thermodynamics, published before 1990, at least, have a circular nature, *i.e.* they show the absence of internal contradictions in our current views, but nothing more and nothing else, because all accessible initial presuppositions (statements) already include in themselves the final statement in a more or less masked form).

The second law of thermodynamics remains an experimental observation, and the entities in the ideation space, the entities that comprise a computably non-enumerable set, are an experimental observation as well. The idea that the entities in the ideation space comprise a computably non-enumerable set was discussed by Henri Bergson in 1901 and 1904 (*Psychophysical Parallelism and Positive Metaphysics*, report and its discussion on May 2, 1901[40]; *The Psycho-Physiological Paralogism*, a lecture to the Congress of Philosophy at Geneva in 1904[41]), however Bergson did not use the term "ideation space", he was using the term "reality" instead, but all his illustrative examples are pointing out that he was keeping in his mind the same part of reality that was called later "ideation space" or space of "religious idealism".

Bergson also has pointed out that anyone set of objects in the brain (neurons and neuronal groups) can correspond to several or many sets of entities in the ideation space (and we know now that these sets in the ideation space are not computably enumerable; and we know now that the above-mentioned neurons and neuronal groups in the brain can serve only as a reminder for some group of computably non-enumerable sets in the ideation space).

Darwinism, as long as it is known, was always criticized from the following position: any novelty, in order to be selected, should be already complete to some extent. *I.e.* it should produce at least some positive effect. Ludwig Büchner, whose book "The Force and Matter"[24] in its first edition was published before "The Origin…", namely in 1855 ("The Origin…" was published in 1865)[30], but the last edition was published after the publication of "The Origin…", in the last edition has mentioned that natural selection is, probably, an important part of nature, but it cannot be the only one or the sole mechanism of evolution. Leo S. Berg has mentioned in 1922 in his book "Nomogenesis…"[42] that the initial stages of evolutionary development of many novelties are proceeding on the basis of law, but not by means of natural selection, because the last one is technically impossible at these early and functionally incomplete stages (an incomplete development of many organs are functionally useless).

However an entity that is in search by an action acceptor can be incomplete in several generations or it can be completed by chance with a help of stochastic mechanisms only in several random generations in some periods (not constantly) of their existence. And what is more, an action acceptor itself can exist in material world only in the form of its own reminder. This reminder can be strong or it can be weak and incomplete. But the incompleteness of this reminder will not prevent from the appearance in the ideation space the corresponding entity that can help to select material entities in accordance with particular action acceptor. The interaction of the material space with the ideation space and the ideation space itself provide an opportunity for evolution and ontogenesis to work with an incomplete solution and with an incomplete action acceptor. And this observation could be the most important in the whole story: an incomplete solution and an incomplete action acceptor are not an exception, but are normal/regular/typical situation for evolution by means of interaction of ideation space with space of vulgar materialism (our 3D physical space).

We would like to finalize our text with two relatively short summaries. One summary concerns our views on evolution and ontogenesis in view of contemporary vulgar materialism (the only possible "scientific" view in accordance with declarations of its proponents). Another summary concerns hybrid vigour and hybrid dysgenesis and here our views are also incompatible with propositions of contemporary social demagogues.

Contemporary evolutionary and ontogenetic views are based on presupposition that there is no other reality than the material one, the reality that can be investigated by means of physics, chemistry and molecular biology. In accordance with these views, an ideation space together with all its equivalents was solely invented by humans, and it has no value for evolution and ontogenesis. Human ideas are just a direct consequence of molecular and other material processes in human brain. Human music can be written on sheets of paper, and even if some talented player can add something during his "performance" (we, on the other hand, avoid the term "performance" where possible: humans are playing music), these deviations can be recorded by a microphone together with supplementary electronic means and they can be kept in an objective material form.

Our evolutionary and ontogenetic views are the opposite – from their beginning up to the end. An ideation space is real for all living creatures, for all creatures those have an anticipated future. Music cannot be written on sheets of paper – what is written is just a symbolic reminder about music. Music can be recorded by technical means, this is an indisputable observation. However the real event in the life of music is an interaction with the consciousness of a listener. And the consciousness of a listener (together with all his experience, his remembered past and his anticipated future) cannot be excluded from the life of any particular musical episode. When we are listening to music, we are listening to a soul of another person, even when we are playing ourselves. We can say this way: when we are playing, we are the authors and we are listening to the soul of our hero, the soul of the character of this musical piece. We do not hear a sequence of notes (it would be absolutely not interesting), but we are listening to a soul of another individual.

Human brain does not contain memory (or remembered past together with anticipated future) – it contains only reminders, symbolic reminders, those are fully material, but those are not equal to remembered past or anticipated future. There could not be any "parallelism" between material space of human brain and ideation space, because the computably non-enumerable set of entities in the ideation space cannot be unambiguously projected to the computably enumerable set of physical entities in the volume of human brain.

Both ontogenesis and evolution of all living creatures are driven by action acceptors – by the entities that are intermediate between ideation space [which includes both anticipated future and remembered past] and space of vulgar materialism [neurons, genes, dsDNA and absolutely all randomly appearing entities in the material world]. Evolution goes through interaction of ideation space with material one. For simplicity we can even say that the evolution is driven by an ideation space [however here we should remember that the ideation space is not appearing from absolute vacuum – material reminders are important for real, but not purely material, world]. Only religious Jews can understand the essence of evolution. Non-religious Jews are following the thought-style of vulgar materialism.

Contemporary views on hybrid vigour and hybrid dysgenesis are comprised by a self-propelled propagation of copy-pasted views, produced by individuals with zero personal experience in breeding of laboratory or any other animals, and these views can be based on any arguments, except direct observation of phenotypes, obtained in different crosses. Speculations of psycho-pharmacologists are fantastically funny. Humans, as a rule, do not recognize the biological difference between an inbred strain and an outbred stock. They know, at the level of definition, that an inbred strain can be reproduced by brother × sister mating; and that during reproduction of an outbred stock any brother × sister mating should be avoided literally at any cost. However they assume that both physiologically and biologically an outbred stock should be about the same as an inbred strain, but a little bit more dirty in its genetic background, whereas all other features of an inbred strain and an outbred stock should be about the same.

In the case of dogs there is popular term "pure breed". It contains nothing wrong in itself, but humans have a tendency to assume that a "pure breed" is something like an inbred strain of mice, and they are very surprised when the cross of one old "pure breed" and some other also well-known "pure breed" produces no expected hybrid vigour at all, but a phenotype that resembles the phenotype of the first four generations in production of a Bengal cat (that is a hybrid between domestic and wild cats, backcrossed to domestic one; hybrid females are crossed to domestic males in this backcross; hybrid females have less health-related issues than hybrid males in any corresponding generation – this is a known consequence of better canalization of ontogenesis in females than in males in general). This is typical hybrid dysgenesis that includes multiple health-related issues – it results in significantly decreased lifespan. Any work with breeding of cats is expensive and requires fanatic enthusiasm in order to be done (please, note that some statistical significance is always desired, and this along requires quantities of animals in both control and experimental groups). Fortunately, hybrid dysgenesis can be observed in guinea pigs: there are known good laboratory outbred stocks of guinea pigs and wild guinea pigs are also readily available[43].

During ontogenesis of any hybrid animal, or ontogenesis of any animal from an outbred stock, multiple action acceptors are trying to build up the best possible phenotype using available genetic factors and using random events of ontogenesis itself those are always present in any ontogenesis.

An excess of genetic novelty that could be a result of hybridization entails the same processes of compensation, including transgenerational epigenetic compensation, as it was shown for drug treatment. The transgenerational epigenetic compensation was first observed as a result of paternal drug treatment – prenatal, neonatal or adolescent drug treatment (L-thyroxine, morphine, *etc.* treatment). The phenotypic result of transgenerational epigenetic compensation of paternal drug treatment could be so-called "phenotypic inversion" – the opposite phenotypic changes in the drug-naïve descendants, obtained from drug-treated fathers, with respect to phenotypic changes induced by the drug treatment itself (in originally normal animals, *e.g.* in their fathers).

The consequences (or the "tail") of transgenerational epigenetic compensation can propagate up to 6-12 generations and their length depends on many factors, including purely stochastic ones. It is safe to assume that starting from the 10^{th} generation all epigenetic processes would be completely stabilized (in the case of mild paternal drug treatment everything can be stabilized even faster – up to 3-4 generations; the same estimation remains true for hybridization – for example, the 5^{th} generation of Bengal cats is considered to be more or less acceptable from the practical standpoint).

In any outbred stock there is always some rotation of genetic novelty, and the processes of self-adaptation and self-compensation, including transgenerational epigenetic compensation, are always self-trained to some extent. There are no such processes in an inbred strain (wherein the developmental noise is always present, however). That is why any good outbred stock cannot be imitated by an inbred strain, or by a group of 2-3 different inbred strains, kept separately.

Any significant genetic disturbance, like an outcross, requires 6-12 subsequent generations (typically – backcross generations) for complete stabilization of phenotype, in order to avoid unstable and destabilized phenotype. However humans prefer solid numbers instead of diffused "intervals": let's say "10 generations".

We cannot avoid possible projection of these results to human population. Only narrow nationalism can serve as a basis for further human evolution. Crosses between different nationalities should be avoided as much as possible. One can say that an event of outcross can be beneficial for population once in 10 generations of particular line. However these 10% of events are not optimal, but maximally allowed value. In real life such 10% could be achieved due to unavoidable random events. Once again we would like to repeat that crosses inside any given nationality are biologically beneficial, whereas crosses between different nationalities are biologically disruptive, however they can produce from time to time some "interesting" (*i.e.* "funky, unusual") phenotypes. Once again we would like to repeat the following facts of hybrid dysgenesis in animals: decreased life-span, over-reaction of immune system, instability of nervous system, problems with digestion, and sometimes problems with reproduction (relatively rare, fortunately, in comparison with over-reaction of immune system), and instability of many regulatory systems during life-span of a given individual.

The same should be true for humans. Indeed, with respect to life-span we all know that individuals with the longest life-span belong to historically old nationalities and there are no hybrids among such individuals. It is interesting to note that among mid-sized dogs the historically oldest breeds demonstrate longer life-span than historically relatively recent breeds (despite some known genetic "problems" in some historically old breeds).

Different allergies among humans are wide-spread today. This over-reaction of immune system must be a result of hybridization, but not a result of water or air pollution, or food additives ("artificial" chemical additives), as it is commonly assumed.

Phenotypic inversion is promoted by transgenerational epigenetic compensation through activation of previously dormant genetic loci (this activation is manifested as dominant traits) and through deactivation of some previously normally expressed genes (this deactivation is manifested as recessive traits and it is relatively difficult to observe it in the experimental crosses those are usually done between "control" and "experimental" animals; one half of "control" genome makes such recessive change practically invisible in this descendant).

Note that phenotypic inversion was experimentally observed not only in the progeny of drug-treated males (in the case of inbred strain – DBA/2J mice (Fig. 4b[7]) and outbred stocks – Sprague-Dawley rats (Fig. 4a[7]) and Wistar rats (Fig. 4c[7]), but also in the progeny of hybrid animals (hybrid guinea pigs, *i.e.* hybrid between two outbred stocks). If the hybrid animals are numbered as F_1 and if among them there is an animal with unusual phenotype, the further cross between this "unusual" animal and "normal" one, the cross that is numbered as F_2, can demonstrate phenotypic inversion – the opposite quantitative changes comparatively to "unusual" F_1 phenotype (see, for example, Fig. 1[13]).

Our article is written about experiments with animals. However some projections and extrapolations to human population are logically unavoidable – due to this reason we would like to provide insight into the matter of human biological evolution.

The term "human evolution" defines all changes in morphology, genetic background, physiology and behaviour, associated with the origin of Negroid, Caucasoid and Mongoloid races, as well as all smaller-scale changes, associated, for example, with such events as domestication of animals and plants, or with the beginning of exploitation of domesticated animals as a working force in agriculture. In the evolutionary biology the terms "black", "white" and "oriental" with respect to human races are avoided as "folkloristic" and imprecise. It is estimated that Negroid human race has originated from apes about 6.5M years ago – this estimation was obtain during previous century (XX) on the basis of protein and DNA sequences – and the precision of this estimation still remains rather questionable (*i.e.* this value should be taken into account with precision +/- one or two millions of years, to be on a safe side). Caucasoid race has originated from Negroid one 113000 years ago (+/- 34000 years). Mongoloid race has originated from Caucasoid race relatively recently – only about 41000 years ago (+/- 15000 years). The above-mentioned results were obtained during the last quarter of previous century (XX) and they were summarized, for example, by Masatoshi Nei in his review published in 1985 (Nei, 1985)[44]. Further discussion can be found in the publication (Vyssotski, 2013)[7], see its "Supplementary Information" for details of human evolution.

Some categories of human behaviour, those are considered today as "socially unacceptable" or even "absolutely unacceptable", played very important or even "leading" role in human evolution during known periods. One of the most important factors (but not the only one) in the origin of Mongoloid race was paedophilic behaviour. Some researchers assume that human evolution in general can be explained by paedomorphism (Gould, 1977[45]; Montagu, 1981[46]). Mongoloid anatomical changes could be explained by the phenomenon of neoteny, whereby an infantile or childlike body form is preserved in adult life (Gould, 1977)[45]. Paedophilic behaviour was an important factor in human evolution in general and one of the most important factors in the origin of Mongoloid race.

It is necessary to note that current statements of social propaganda cannot do paedophilic behaviour less natural or less important for human evolution. It is good to remember when we would like to think, for example, about known behaviour of Konstantin S. Mereschkowsky, a researcher who has discovered and described the symbiotic origin of intra-cellular organelles of eukaryotic cells from bacteria (1905)[47] and the author of book "*Earthly Paradise, or a Winter Night's Dream. Tales from the 27th century*" (1903)[48].

The concept of symbiogenetic evolution, as well as any symbiosis or endosymbiosis in general, cannot be understood on the basis of evolution by means of natural selection. However symbiosis is appearing semi-automatically, if evolution is driven by action acceptors. Action acceptors can search for and can hold (at the beginning – mechanically) any entity, independently of its size (even if is an independent organism), if this action is useful. Action acceptors are searching for local positive results and not for elimination of all competitors or elimination of all other organisms that are moving (are still alive) Personally, Mereschkowsky did not believe into the theory of natural selection, he has seen it as an erroneous concept, as well as Danilevski did (1885)[49-51].

Contemporary social propaganda and the laws, based on it, are known to be promoting a set of false statements in the field of sex equality, race equality, and currently it promotes biologically disruptive behaviour such as inter-racial breeding (without any knowledge of hybrid vigour and hybrid dysgenesis). Hybrids can have increased body weight at given age, but, simultaneously, they typically have decreased lifespan, over-reaction of immune system, unstable/destabilized expression of batteries of genes those are supposed to be dormant in parental stocks, and problems with regulation in one or several functional systems, including immune system, nervous system and digestive system (the results of hybrid dysgenesis, known for dogs, cats and guinea pigs, are reported for outbred stocks; for inbred strains, *e.g.* mouse strains, more typical result is hybrid vigour than hybrid dysgenesis). Some of the above-mentioned problems with regulation are not evident in young animals, but are appearing during aging.

"Sex equality" provides another example of contradiction between legal and natural fields of research. Here we would like to compare book of Catharine A. MacKinnon "Sex Equality" (2001)[52], as a representative of law-centred approach, and book of Vigen A. Geodakian "Two Sexes. Why? The Evolutionary Theory of Sex" (2012)[53]. The evolutionary theory of sex was developing since 1965 (Geodakian, 1966)[54-55], but it is summarized in the most comprehensive form in the above-mentioned book (Geodakian, 2012)[53]. In this book it is explained why the vast majority of species on the Earth (animals and plants) are represented by male and female subjects and how the sexual dimorphism (differences between males and females) accelerates evolution of all above-mentioned species, and it not

only accelerates it, but it makes evolution more efficient (the sexual dimorphism increases the ratio of positive effects to cost factors of evolutionary process). On the other hand we have book of MacKinnon (2001)[52] wherein the sex equality is represented as an indisputable goal (among other "equality goals"). It is a difficult task to criticize a book that is a result of more than 25 years of hard work with positive intentions, and that contains more than 1650 pages, but, nevertheless, we have to mention that if the described in this book "sex equality goal" would be materialized (G-d forbid), humans would have about the same rate of evolution as hermaphrodites (which are relatively simple organisms; good examples – an earthworm and tomato). Thus, under the cover of the book "Sex Equality" we have 1650 pages of biologically irrelevant material, the material that is reviewed form the standpoint of initially erroneous goals. It is important to note that the evolution of law is mainly a self-propelled process, independent of external influences, including influences of natural sciences. Cases are cascaded over previous cases – and so on up to the end. In the contemporary society the evolution of law could be proceeding in any maladaptive direction, including dangerous ones (it is sufficient to have several "indisputable goals", like an "equality goal", promoted by social or other demagogues, – the rest is going on automatically).

"Race equality" is another famous (or infamous?) example of contradiction between evolutionary biology and contemporary law. Statistically significant differences can be obtained between Negroid, Caucasoid and Mongoloid races practically in any trait (and it is much more difficult to find a trait that does not show statistically significant differences). Sexual behaviour is not an exception from general rule. Under the conditions of normal society (it means that the army, correction departments, ships and similar facilities are excluded from consideration) and under relatively weak social pressure in the field of sexual behaviour (like, for example, in Switzerland, Holland and Thailand) the percent of individuals, demonstrating homosexual behaviour, is different for Negroid, Caucasoid and Mongoloid races (hereinafter we take into account only male homosexuals; lesbians comprise separate data set). The lowest percent of homosexuals is among Negroid race (about 2.5%), the next goes Caucasoid race (about 5% of homosexuals – this is very well known number, but it is associated typically [and erroneously, of course] with human population "in general"), and Mongoloid race is the most homosexual one (up to 8.8% of homosexuals, in accordance with known estimations). This can be confirmed at the level of human culture as well. Some Korean movies that exist only in Korean language, without English translation, illustrate both facultative homosexuality and the role of Christian propaganda in perception of this phenomenon in Korean society. The border between "facultative" and "exclusive" homosexuals is diffused, even for such classical example as Peter Tchaikovsky (it is known that he was married and, thus, could be formally considered as a "facultative" homosexual). Leonardo da Vinci comprises another famous example, but an example of "exclusive" homosexual. Paedophilic behaviour comprises also a point of interest, but statistical data for Negroids, Caucasoids and Mongoloids with respect to paedophilic behaviour are not available for general public (as well as other nationality-linked and race-linked crime-related data) and, thus, it cannot be discussed in numbers. However there is no doubt that the distribution of paedophiles among Negroid, Caucasoid and Mongoloid races resembles the above-mentioned distribution of homosexuals: the lowest percent of paedophiles are among Negroid race, some intermediate percent of paedophiles – among Caucasoid one, and the highest percent of paedophiles – among Mongoloids. From the standpoint of evolutionary biology, if paedophilic behaviour is considered as an "X", then the whole Mongoloid race should be inevitably considered as a direct product of this "X". Now, if normal behaviour is statistically different for different races, which one should be taken as a basis for "our humanistic law"? The law that should be "one for all" in accordance with contemporary social propaganda! Should the law be optimized for Negroid, or Caucasoid, or Mongoloid race, or it should be optimized for some statistically averaged value? This question cannot have any satisfactory answer in the frame of current legal thought-style.

From the standpoint of social thinking it is often assumed that the absence of equality will inevitably lead to the elimination of "less fit" individuals, nations and races. This thought-style is known as "social Darwinism". However our perception of this thought-style is based on the assumption that Darwinism comprises the main and the only possible mechanism(s) of organic evolution. Imagine: natural selection is true as a scientific theory (because this process can be observed in the wild and semi-natural populations) and, simultaneously, Darwinism is a deeply erroneous evolutionary thought-style, because it does not contain the most important action-acceptor-driven group of evolutionary mechanisms[13]. "Evolution" cannot be used as a synonym for natural selection and *vice versa*.

It is also nice to know that natural selection and Darwinism in general were serving as a solid scientific basis of ideology of Adolf Hitler, adding scientific objectivity to his thought-style, expressed in his famous and simultaneously infamous book *Mein Kampf* (Edition for reference – 1938; see, for example, Part 1, Chapter 4 "Munich")[56]. Narrow nationalism and Darwinism have formed the core of Hitler's thought-style and Hitler's teaching. In his "creative synthesis" the erroneous part was assumed to be a narrow nationalism, whereas Darwinism was assumed to be "OK". Narrow nationalism consists of restriction of crosses between different populations and sub-populations (different races and nationalities in humans), and it was known well before Hitler and it contains nothing more (see, for example, discussion in: Danilevski, 1885)[49-51]. In a biological dimension the narrow nationalism concerns questions about hybrid vigour and hybrid dysgenesis that are interesting *per se*r. Darwinism, as a thought-style that declares natural selection as an exclusive mechanism of evolution of humans and other species, is the erroneous part of Hitlerism (this is just a historical remark – we are not proponents of A. Hitler, of course, in view of all known deeds of Hitlerites).

One more interesting text, known as "*Protocols of the Elders of Zion*" (Edition for reference – 1922, Berlin, with introductory comments written by Winberg; this is Russian edition, see reference below), does not produce any negative consonance, if Darwinism is eliminated from human's thought-style.

Protocols of the Elders of Zion (RiverCrest Publishing, 2011)[57]. Dated (presumably) 1897. [There is also Russian language edition, published in Berlin in 1922, and it is much better, with introduction and comments: *Протоколы Сіонскихъ Мудрецовъ. (по тексту С.А. Нилуса) Всемірныи Тайный Заговоръ.* («Прессе», Берлинъ, 1922)].

The title itself was associated with this text *post hoc* and it is not an original part of the text. The author or editor of these protocols remains unknown. The text was found written in French. In the introduction to the Russian translation, published in Berlin in 1922, it is pointed out that the most probable author could be Asher Ginsberg [Ашеръ Гинцбергъ]. This hypothesis is based on some similarities in the contents of the published works of the above-mentioned author and the text of "*Protocols*…", as it is claimed in the above-mentioned introduction. However such compilation could be done as well by a third party (by an unnamed independent person/editor). In 1999 it was claimed that the most probable editor of "*Protocols*…" could be Matvei Golovinski. This claim was based on secret documents, stored and found in Russia. Both hypotheses (about Ginsberg's direct or indirect authorship and about Golovinski's editorial work) could be true simultaneously: 1) both Ginsberg and Golovinski had sufficient knowledge of Russian language to use Russian-style word combinations in a French text; 2) some pieces of the text (of its instructive part) could be written only by a person who was unfamiliar with works, known in the field of economics, including those that were written 50 years ago (by Pierre-Joseph Proudhon[31] and Karl Marx[32], published in 1847), and this person definitely was not Asher Ginsberg (*i.e.* the final version of this text was not edited by Ginsberg); 3) other parts (mainly observational ones) could not be written by Matvei Golovinski himself, even with all his possible knowledge of Dostoevsky's works (some pieces of the text are pointed out that the author or editor of "*Protocols*…" was familiar with publications of Dostoevsky; some other parts have similarities with less famous texts, written by authors, not so popular at that time).

The synthetic nature of the text of "*Protocols*…" is well known: it is comprised from several independent sources or texts with different thought-styles. Some of its pieces with mainly instructive contents have obvious non-Jewish origin, whereas some other pieces with mainly observational contents… we cannot say the same about all these pieces, and the text in general is very interesting. "By so much as ours disregard success if only they can carry through their plans. By so much the goyim are willing to sacrifice any plans only to have success" (from Protocol XV)[57]. Note that the plurality of thought-styles in the frame of the above-mentioned document does not provide an answer to the question whether this document is "false" or "real". The analysis of text cannot even provide an answer to the question about the number of authors, in view of known dialogical novels of Dostoevsky, because each of them contains in itself several incompatible thought-styles, whereas it is clearly known that each of these novels was written by one person – Fyodor Dostoevsky (Bakhtin, 1929, 1963)[58]. Thus, we know that at least sometimes one person can be a carrier of several incompatible thought-styles, and can handle these thought-styles with great passion.

However, anyway, why we are speaking about some strange texts, instead of providing direct references to the primary ones? The answer is self-evident for those who are familiar with them. For those who are interested in, but not so experienced with language, I would like to point out to the English translation, prepared and published in 1962[38]. Sometimes, in some places, it is more controversial than, for example, the Chabad English translation (currently present at www.chabad.org), but for those who would like to get some sort of functionality-related intuition, the translation of year 1962[38] could be more helpful (look, for example, at the end of the Second Commandment, and compare both versions of translation).

Concerning "*Protocols*…" and its instructive part, promoting centralized power and centralized system in general, – it is just a joke. May be we will never know for sure who and what for has introduced this joke into the text, but its provocative power is impressive for those who do not understand that a reticular formation with independent observers/actors is not only more efficient, but more robust, because if no communication exists – nothing can be intercepted and interpreted. In such formation an "external command" is always obtained by means of observation – it is legally absent, but its function is present. And the primary actor is usually not the one who is the most powerful or the most famous, but the one who has the best position for attack/action. Was his mind directed by G-d? Who knows? This is an idealized situation, of course… As it is written in the conclusion of the article "Nomogenesis and the logic of chance" (2016)[13]: "There are no analytical means that could distinguish… the results of the above-mentioned process and the results of evolution, directed by G-d, if our understanding of G-d is provided by Orthodox Judaism".

The negative impact of Darwinism, vulgar materialism and a thought-style that is called now "scientific" is so strong (and these entities are so closely linked) that it does not matter whose goatee head will be a battering ram, will occur at the tip of the battering ram that will make a breach in this structure. And it does not matter from which side this breach will be done. The structure that is called now by some people a "creative synthesis" must be drowned at any cost. It should be done, because any behaviour, ontogenesis and evolution of living organisms can be understood only as an interaction of the ideation space with the space of vulgar materialism. Whereas the contemporary structure of scientific knowledge in natural sciences does not allow even a though about one non-material object, let alone a computably non-enumerable set of non-material objects. In addition, the ideation space has a computably non-enumerable number of dimensions (a multi-dimensional space, wherein it is impossible to determine unambiguously whether it is a two-dimensional, three-dimensional or n-dimensional space). The contemporary mathematical analysis, at least as it is widely known, works well only with computably enumerable sets. And actually even for uni-dimensional space, if the set of objects in this space is not a computably enumerable one (the objects cannot be numbered 1, 2, 3 and so on unambiguously and they cannot keep/retain these numbers), the application of contemporary mathematical analysis is problematic, to put it mildly. The material objects can be numbered readily (as a rule). The situation with non-material objects is more complicated, but these non-material objects do not become due to this reason less important or less real. Our reality includes in itself both the space of vulgar materialism and the ideation space.

Darwinism that declares natural selection as the most important mechanism of evolution is an erroneous evolutionary teaching. However the opposite statement, namely that natural selection "does not exist", would be also a deep error. Any nationality evolves due to internal action-acceptor-driven processes and the elimination or destruction of other nationalities

plays a minor and always secondary role in evolution of any given nationality, and sometimes it does not play any positive role at all. That is why narrow nationalism, Zionism and religious idealism are the basis of human evolution.

Evolution on Earth was driven by action acceptors from the early beginning, before the appearance of DNA replication and before the appearance of co-variant reduplication in general. However this fact was not recognized until recently – it was discussed only in 2016[13].

Before the appearance of more or less reliable reduplication, action acceptors were collecting useful components from the environment. Action acceptors were also collecting themselves (*i.e.* they were collecting the entities resembling these action acceptors, but these entities were borne in their common environment by chance).

Action acceptors indeed can collect components that were borne by chance, but the last one does not mean that all these components always must be borne by chance. Later in evolution action acceptors were also collecting all components that were increasing the probability of appearance of useful components and all this staff was collected and held together – that was the condition that has helped to hold together DNA-replicating proteins, original substrates and more or less final products. Action acceptors were collecting more or less successfully replicated copies, partially compensating for extremely low reliability (a lot of errors) of replication at the earliest stages of evolution.

Some old evolutionary concepts that were rejected by the contemporary "scientific knowledge" as erroneous ones should be reconsidered in view of action acceptors. Among the above-mentioned evolutionary concepts we would like to point out to the theory of germinal selection, developed by August Weismann and published in the article "On the germinal selection as a source of definite variation" in 1904[59]. This theory exists now in the form of "gametic selection", wherein gametes with different genotypes are thought to have different probability in their further history (different probability of participation in zygote formation). Weismann's concept differs from the germinal selection: he assumed that not only whole gametes could be selected, but their smaller parts could be selected as separate units also, before the formation of each gamete. Weismann supposed that "the strongest" elements could be selected, assuming the existence of a process that is something like micro-natural-selection, wherein the strongest elements are going to be selected and kept for further processing.

Now we can say that not "the strongest" elements will be selected, but the elements that will be chosen by action acceptors. And we know that action acceptors can be relatively simple, they could have, paradoxically, more simple construction than the entities that are going to be selected or collected with a help of the above-mentioned action acceptors.

The second important notion is that an action acceptor can use for selection only some relatively small part of each selectable entity, for example, if the selectable entity is a protein, it is not absolutely necessary that action acceptor, used for collection of this protein, will use the biologically active part of this enzyme – it could use its spatially relatively small part, that is not its catalytic centre, to collect it in view of other proteins or all other available entities.

The third notion is that the part of an entity that is used for its collection and its really useful part could be different in their origin and material. For example, it the selectable entities are pieces of dsDNA, their selection could be done using DNA methylation marks or even proteins, more or less reliably associated with this collectable dsDNA.

And it is important to remember that it could be (should be / would be) a plurality of mechanisms, those are not mutually exclusive, those are working together, and all of them are based on the action acceptors, co-existing simultaneously.

P.S.: This Supplementary Information consists of two parts, those are very different both logically and emotionally: 1) the first one is about an anticipated future, action acceptor, purposive behaviour, ideation space and interaction of ideation space with our material reality; 2) the second part is about hybrid dysgenesis, narrow nationalism, Adolf Hitler, *Protocols of the Elders of Zion* and similar matters.

I like the first part very much, probably as any other human being. Its logic is dictated by ideation space and it is very bright part about the anticipated future, very emotionally positive. I hate the second part, wherein the excess of genetic novelty entails such problems for ontogenesis that the last one cannot handle them with positive outcome. This part and its logic are determined by material reality. From the side of the ideation space it can be done a lot, always a lot, but, because the evolution is an interaction of the ideation space with the material reality, not any genetic garbage can be utilized, can be sorted out properly. We can speak about ideation space with great pleasure, but we would not like to follow Christian thought-style, wherein the presence of ideation part is combined with the ignorance of material one. Henri Bergson in his last book "*The Two Sources of Morality and Religion*"[60] discussed Christianity as an illustrative example of "dynamic" part of any religion, *versus* "static" part, whose examples were taken by Bergson from ancient religions.

Evolution goes through interaction of ideation space with space of vulgar materialism and the material part could not be ignored (at least, such ignorance would be an error). Not all previously reinforced laws, both in the USA and Germany, are bad by definition. I had similar discussion many-many years ago in Russia concerning Trofim Lysenko. And I have said there and I would like to repeat it here that not all propositions of Trofim Lysenko were erroneous. His idea that there are special and unique biological laws and regularities and that these regularities have control over physical and chemical processes in living systems, despite the laws of physics and chemistry are the same for living and non-living beings, remains in force.

P.P.S.: The most severe problems appear not in the first generation hybrids F_1. In the F_1 maternal and paternal sets of genes are mostly complete without omissions. However in the F_2 and further generations portions of original genomes are represented partially, with semi-random selection of loci, obtained from given races. It means that something could be unbalanced. The most terrible phenotype (disrupted ontogenesis of nervous system) was observed in one almost adult female – in a descendant of Mongoloid female and hybrid male, who was himself the F_1 generation cross of Negroid and Caucasoid races.

Supplementary Methods

1. Animals and enrichment

During postnatal days P22-P60 female mice (C57BL/6J, DBA/2J and their F_1 hybrid B6D2F1) were housed in the cages "Type II L" (365 × 207 × 140 mm) /Tecniplast, Italy/ (standard housing conditions) or "Type IV" (595 × 380 × 200 mm) (enriched); 4 mice of the same genotype per cage. Toys of different nature were placed in the enriched cages and these toys were renewed twice weekly (see sections "Animals" and "Housing conditions" below).

1.1. Animals

We used females of the two inbred strains C57BL/6J and DBA/2J and their F_1-hybrid B6D2F1 from Taconic M&B A/S, Ry, Denmark. Freshly weaned females (C57BL/6J, DBA/2J & B6D2F1) were ordered. 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.

1.2. Housing conditions

Mice were housed under standard and enriched conditions for six weeks minus 4 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 (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.

2. Behavioural Testing

Mice were subjected to 4 standard behavioural tests (all in the same order): day 1 – Elevated O-Maze Test; day 3 – Open-Field Test; day 4 – Novel Object Test; and days 8-12 – spatial navigation in the Morris Water Maze. All tests were run during the dark phase of the cycle (07:00-19:00 h). Test rooms were indirectly illuminated by 4 40W bulbs adjusted to yield 32 lx in the centre of the test arena. Animals were video-tracked in all tests using the Noldus EthoVision 3.00 system (Noldus Information Technology, Wageningen NL, www.noldus.com) which recorded centre point position and subject area at 4.2 Hz. Additional behaviours could be monitored using the built-in keyboard event recorder. Combined data were transferred to public domain software Wintrack 2.4 (www.dpwolfer.ch/wintrack ; Wolfer *et al.*, 2001)[61] for analysis.

2.1. Elevated O-Maze Test

The elevated plus maze test is the most frequently used test to study anxiety-related behaviours in pharmacology and neuroscience (Belzung & Griebel, 2001)[62]. The elevated O-Maze is a modification of the elevated plus maze that has the advantage that it lacks the ambiguous central area of the elevated plus maze (Crawley, 2000)[63].

Apparatus and procedure. A 5.5 cm wide annular runway made of grey plastic with an outer diameter of 46 cm was placed 40 cm above the floor. Two opposing 90° sectors were protected by 16 cm height inner and outer walls made of grey polyvinyl-chloride (closed sectors). The remaining two 90° sectors were without walls (open sectors). Animals were released in one of the closed sectors and observed for 5 min.

Variables. The percent of time spent on open sectors has been chosen as an indicator of subjectively estimated potential danger (in the wild nature such danger would be an appearance of an aerial or terrestrial predator): time spent on open sectors (%) [ITXE]. Hereinafter in square brackets we provide short variable name as it is in use in Wintrack 2.4 – for reference only, to avoid ambiguity.

2.2. Open-Field Test

The Open-Field Test is clearly the most frequently used of all behavioural tests in pharmacology and neuroscience. Despite the simplicity of the apparatus, however, open field behaviour is complex. Consequently, it has been used to study a variety of behavioural traits, including general motor function, exploratory activity and anxiety-related behaviours (Crawley, 2000[63]; Prut & Belzung, 2003[64]).

Apparatus and procedure. Four quadratic arenas (50 × 50 cm, 37 cm height) made of non-reflective white plastic were concurrently used. Mice were placed in the arena for 30 min.

Variables. To assess changes over time related to habituation we calculated changes in the length of path travelled between the first and last 10 min [TPMX_H].

2.3. Novel Object Test

The Novel Object Test is not a very frequently used behavioural test. However, in combination with an open field test, it serves to discriminate between approach and avoidance tendencies towards novel stimuli (*e.g.* Dulawa *et al*., 1999)[65].

Apparatus and procedure. 24 h after the Open-Field test, the animals were re-exposed for 15 min to the same arena. Then, a semi-transparent 50 ml Falcon tube (height 12 cm, diameter 4 cm) was placed vertically in the centre of the arena and the behaviour of the mice monitored for another 15 min.

Variables. An object zone was defined such that the mouse was detected inside the zone by the video-tracking system whenever it was touching the object with at least its nose. Object exploration was estimated by calculating the difference in the amount of small movements (cf. Mohajeri *et al*., 2004)[66] inside the object zone between time period with object (the second 15 min) and time period without object (the first 15 min). It is so called horizontal object exploration [DNSEQUNO].

2.4. Place Navigation in the Water Maze

The water maze, also known as Morris water maze (Morris, 1984)[67], has become the most frequently used tool in the study of learning and memory in mice (D'Hooge & De Deyn, 2001)[68].

Apparatus and procedure. A round swim tank made of poly-propylene with a diameter of 150 cm was filled with water (temperature 24-26°C, depth 15 cm) that was made opaque by adding 1 litre of milk. A quadratic goal platform (14 × 14 cm) was hidden at a constant location 0.5 cm below the water surface. Its centre was always 325 mm from the side of the pool. The mice performed 16 training trials (4 per day, max. duration 90 s) from varying (pseudo random) starting positions, with an inter-trial interval of 30 s which they spent on the goal platform (massed training). To minimize handling, they were transferred to the pool using a white plastic cup and allowed to climb onto a wire mesh grid for retrieval. On day 5, the mice performed a 60 s probe test without the goal platform. Experimental groups, as well as control ones, were divided into four subsets, each with a different target quadrant.

Variables. From training trials, we calculated average escape latency [TIM01X16] as a measure of overall escape performance. In addition, we calculated average swim speed [SPD01X16] and average swim path length [PTH01X16]. From probe trial, we calculated two measures of spatial selectivity: 1) number of crossings of target (trained) annulus [XAT17] (annulus was determined as a square 16 cm on side) and 2) number of crossings over similar zones in two adjacent quadrants [XAC17] (adjacent annuli crossings).

2.5. Sound frequency and sound duration discrimination (Go/NoGo)

Sound discrimination was investigated in 48 mice at the age of 7 months (8 mice per group, the same 6 groups as in the previous tests: C57BL/6J standard & enriched, DBA/2J standard & enriched, B6D2F1 standard & enriched). Sound

frequency discrimination (and, later, sound duration discrimination) was investigated in Go/NoGo paradigm.

Apparatus and procedure. "Mouse Shuttle Box" (Campden Instruments Ltd., UK) was used (Buselmaier *et al*., 1981)[69] for Go/NoGo sound discrimination test. It consisted of a metallic chamber (270 × 115 × 130 mm) with two identical compartments (135 × 115 × 130 mm each; L × W × H), supplied with grid floor. Compartments were separated by the wall with 38 × 49 mm arch opening and were illuminated by 1 W bulb per compartment. Animals at the age of 7 months were trained during 7 days (40 "Go" and 40 "NoGo" trails daily) to discriminate between pairs of sound. The sound pressure level (SPL) was 75 dB in the centre of experimental compartment. In the 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 (the onset of 200 ms current coincided with the onset of the second sound in the sound pair). Inter-trial time interval was varying by chance in the range 5-15 s. 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, 0.20 mA, once. At the moment of current application, "NoGo" sound presentation was terminated even if the animal was not exposed to the whole 5 "NoGo". The order of "Go" and "NoGo" trials was pseudo-stochastic (Lipp & Van der Loos, 1991)[70], but fixed for all animals and all training days. After 7 days of task-free period the animals were tested in Go/NoGo sound **duration** discrimination task during 7 days. "NoGo" signal was taken from 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". All files for sound discrimination were prepared using Sonic Foundry Sound Forge, Version 5.0b (Build 162) (www.sonicfoundry.com) and were recorded at 44100 Hz sample rate, 16-bit bit depth, stereo (two identical channels). "Fade In" (5 ms) and "Fade Out" (5 ms) were applied at the beginning and at the end of each sound. The system consisted of four identical shuttle-boxes (working simultaneously) and each shuttle-box was placed in a sound-insulating enclosure with front opening. The system was controlled by a computer through printer port and audio signal to all 4 speakers was supplied by computer sound card that had build-in amplifier.

Variables. The number of correct responses ("Correct Go", *i.e.* when animal moves from one compartment to another one during "Go" signal presentation series), the number of wrong responses ("Mistaken Go", *i.e.* when animal moves from one compartment to another one during "NoGo" signal presentation series) and the number of "Inter-crosses" (*i.e.* when animal moves from one compartment to another one in time intervals between series of sound presentations, when auditory cues are absent) were recorded. Discrimination D was calculated as D [%] = ("Correct Go" - "Mistaken Go")/40 × 100.

2.6. Visual-tactile and olfactory discrimination (Hole-board)

Visual-tactile and olfactory discrimination was investigated in 48 mice at the age of 11 months (8 mice per group; these mice were used for Go/NoGo sound discrimination task 4 months earlier). Each animal was tested during 5 days, 6 min daily. During day 1 and day 2 it was tested in classic hole-board, during day 3 – in visual-tactile discrimination, during days 4 and 5 – in olfactory discrimination.

Apparatus and procedure. The test system consisted of square 40 × 40 cm 16-hole hole-board with 32 cm walls and nosepoke detectors under the floor (4 infrared beams, 4 channels per box). The signals from infrared detectors were transmitted to IBM PC through printer port. Hole-board had grey polyvinyl chloride (PVC) floor with 16 round holes D = 25 mm, spaced in configuration 4 × 4 with 100 mm step between consecutive rows or columns. The floor itself had thickness 4 mm and cylindrical space D = 72 mm, h = 21 mm under each hole. Plastic Petri dish of above-mentioned diameter was placed under each hole. Illumination was 25 lx in the center of arena. During day 3 (visual-tactile discrimination) each second row of holes was replaced with beech plywood floor, natural colour, thickness 4 mm, with 6-point star holes, each side of equilateral triangle 30 mm. During day 4 (olfactory discrimination) only PVC floor with round holes was used, but under the ½ part of the floor in the each hole 1.4 g of dried powder of Mint (*Mentha piperita*, that is hybrid [*M. aquatica* × *M. spicata*]) was added. Specifically, the "Mint Tea" sold under "Migros" brand (Switzerland) was used (the contents of one tea bag was placed into a Petri dish, the bag itself was discarded). In accordance with manufacturer's description each above-mentioned portion consists of 1.4 g of dried powder of Mint (*Mentha piperita*, that is hybrid [*M. aquatica* × *M. spicata*]). During an experimental day the Mint in the Petri dishes was replaced each 4 hours to keep it fresh (each bag of Migros "Mint Tea" is individually factory sealed). During day 5 the protocol of olfactory discrimination was applied the second time (*i.e.* day 5 is a replication of day 4).

Variables. The following three indicators of behaviour were registered with a help of IBM PC during 6-min session: a) total number of nosepokes; b) total duration of all nosepoke activity (total exploration time); c) mean duration of a nosepoke (c = b/a). During visual-tactile and olfactory discrimination the above-mentioned indicators of behaviour were recorded and analyzed for each row separately. Visual-tactile discrimination D was calculated as D[%] = ("New" - "Old")/("New" + "Old") × 100, were "New" and "Old" – total exploration time of new and old holes. Olfactory discrimination D was calculated as D[%] = ("No-odour" - "Odour")/("No-odour" + "Odour") × 100, were "No-odour" and "Odour" – total exploration time of holes without and with Mint odour. Olfactory discrimination during day 4 (the first day of olfactory discrimination) is shown in the **Fig. 3d**.

3.1. EEG (auditory event-related potentials) recording

EEG recording was done in 48 mice at the age of 7 months (6-8 mice per group, typically 8). These mice were never used for any sound-discrimination in any experiment. Their EEG was recorded exactly at the same age as the age of Go/NoGo training of independent subset of mice (in sound discrimination task).

Apparatus and procedure. Briefly, the recording electrode was placed 2.7 mm posterior to bregma, 3.5 mm to the right of the midline, reference – on the same hemisphere near the right olfactory bulb. Auditory stimuli (75 dB SPL) were presented in 4 independent sets. In the first set the stimulus was accord 4 + 8 kHz, duration 50 ms, inter-stimulus interval (onset-to-onset) 500 ms. The record duration was optimized to have 2700 presentations of stimulus in a set (*i.e.* about 25 min). In the second set the stimulus was accord 3 + 6 kHz, duration 150 ms; in the third – accord 3 + 6 kHz, duration 50 ms; in the fourth – accord 4 + 8 kHz, duration 150 ms. Four consecutive sets were separated by 3-5 min sound-free time intervals.

3.2. Animal preparation

Animals were anesthetized with ketamine-xylazine (87 mg/kg ketamine + 13 mg/kg xylazine, i.p.). Surgery was performed with a help of Stoelting Lab Standard™ Stereotaxis (www.stoeltingco.com) with World Precision Instruments Mouse Adaptor #502062 (www.wpiinc.com). Skin over the scull was removed, the scull surface was prepared using H_2O_2 (30%) and ethanol (91%). Five small burr holes of 0.8 mm diameter were drilled in the scull, two over the front, one at the back of the scull and one each over the estimated location of the auditory cortex (approximately 2.7 mm posterior to bregma, approximately 3.5 mm to the left/right of the midline). Five gold-plated screws were then carefully inserted (two of them – signal electrodes from the right and the left auditory cortex; two more [front left and back] – two grounds; and the right front – reference). Prior to the operation miniature coaxial connectors (MK01/50G, www.distrelec.ch) had been coaxially soldered onto the head of these screws (screwdriver slot was made on the top of each connector before soldering procedure; each connector looked like very small gold-plated tube with internal diameter 0.5 mm and closed bottom; external diameter and length were 1.55 mm and 3.9 mm respectively; the bottom was soldered onto the screw head). Great care was taken not to injure the brain during the drilling or insertion of the screws. The screws were then fixated with dental cement ("Paladur"). Antiseptic "Merfen" (powder, produced by Novartis, 1 g contains 5 mg Chlorhexidingluconat, Benzoxoniumchlorid) was applied around dental cement immediately after operation. The animals were allowed to recover for 6-12 days from the operation before the first EEG recording. All records shown in this article were obtained from the electrode in the right auditory cortex – from the same hemisphere, in which the reference electrode was placed. Both electrodes were used for statistical analysis.

3.3. Auditory stimuli

Auditory stimuli were generated with a RP1 system (Tucker-Davis Technologies, Alachua, FL, USA), amplified with PA5 amplifiers (Tucker-Davis Technologies, Alachua, FL, USA) and delivered through two electrostatic loudspeakers

(Tucker-Davis Technologies, Alachua, FL, USA) mounted at an approximate height of 5 cm in the two short sides of the recording box. Stimuli were of an approximate SPL of 75 dB.

3.4. EEG recording

EEGs were recorded in a plastic box (length 356 mm, width 183 mm, height 345 mm; internal size) placed into rectangular grounded copper box with a lid serving as a Faraday cage. An animal was insulated from the Faraday cage by the internal plastic walls and plastic floor, covered by tissue paper. Copper lid was slightly shifted for 1-2 cm to provide necessary ventilation and light (it was relatively dark in the chamber, but it was not absolute darkness). Miniature plugs were connected to the connectors mounted on the animal's head. For facilitation of the connection procedure an animal was slightly anaesthetized by inhalation of Methoxyflurane ("Metofane") vapour. Two electrodes over the back and front of the scull served as ground electrodes, one electrode over the front of the scull (right) as reference electrode, one electrode over the left auditory cortex and one electrode of the right auditory cortex served as active electrodes (**Supplementary Fig. 2**). The miniature plugs were connected to a swivel joint connector allowing the animal free range of movement. The EEG was amplified with a Siemens Mingograf 21 EEG amplifier (band pass filter 0.1-200 Hz, 50 Hz notch filter) and digitized with a Biopac M100 (Biopac Systems, Goleta, CA, USA) system at a rate of 500 Hz. The raw EEG was continuously stored on a computer disk along with digital stimulus tags.

Data processing was performed off-line with the help of Neuroscan software Version 4.2 (Compumedics, El Paso, TX, USA) using Dell Precision 650 workstation. For the analysis of the auditory ERPs, epochs were constructed that consisted of a 100 ms pre-stimulus baseline and 800 ms post-stimulus interval (800 ms from the onset of stimulus). Epochs in which amplitudes exceeded ± 100 μV at the two active electrodes were excluded from further averaging. Data obtained in this study were detrended. Following artifact rejection, epochs were averaged off-line for each animal and paradigm separately.

4. General statistical analysis

Data were analyzed using Mann-Whitney U-test. This non-parametric test can be applied to bimodal and multimodal distributions (contrary to parametric methods, which can be used if and only if the data meet assumptions of normality and homogeneity of variances). The possibility to analyze data with bimodal and multimodal distributions allows to pool appropriate groups from different laboratories and different replicates, if the number of animals in each control and experimental group is about the same in each lab and/or replicate. Using Mann-Whitney U-test all standard C57BL/6J were compared with all enriched C57BL/6J, all standard DBA/2J – with all enriched DBA/2J, all standard B6D2F1 – with all enriched B6D2F1. 2-way factorial ANOVA model with between subject factors housing condition (standard versus enriched housing) and genotype (C57BL/6J, DBA/2J, B6D2F1) was applied for illustrative purposes only (see, for example, **Supplementary Fig. 10c-f**), being one of the most commonly used statistical methods.

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