

Cross-species analyses of intra-species behavioral differences in mammals and fish

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Abstract

Multiple species display robust behavioral variance among individuals due to genetic, genomic, epigenetic, neuroplasticity and environmental factors. Behavioral individuality has been extensively studied in various animal models, including rodents and other mammals. Recently, fish, such zebrafish (*Danio rerio*), have emerged as powerful aquatic model organisms with overt individual differences in behavioral, nociceptive and other CNS traits. Here, we evaluate individual behavioral differences in mammals and fish, emphasizing the importance of cross-species analyses of intraspecies variance in experimental models of normal and pathological CNS functions.

Keywords: Individuality, behavioral traits, animal models, mammals, fish, zebrafish

Introduction

Experimental (animal) models are a powerful tool for neuroscience and biobehavioral research [1-3]. In addition to utilizing animals as *models* of normal and pathological biological processes, some species are particularly commonly used in biomedicine (due to their practical ease, genetic tractability and other advantages), often conceptualized as ‘model organisms’ or ‘model species’ [4]. Like humans, various animal model species display robust behavioral variance among individuals, presenting consistent (stable) behavioral traits that vary between individuals from the same species/group [5-8]. Genetic, genomic and epigenetic mechanisms, as well as neurodevelopmental, neuroplasticity and environmental factors potentially modulate individual behavioral traits in various organisms [9-12]. In laboratory settings, individual behavioral variance can be reduced by standardizing some general housing and experimental conditions or by using more homogenous (e.g., inbred vs. outbred) animals and/or their populations (e.g., same-batch, same-supplier) [13]. However, individuals of even the same strain may display remarkable variance in their behavioral responses to the identical stimuli in standardized laboratory conditions [6]. Moreover, standardizing laboratory conditions does not always reduce, and may even promote, variance in animal behavioral models [14][19333241], thus complicating the reproducibility of preclinical animal research [29470495, 28448068].

Initially treated as an unwanted ‘noise’ in behavioral data, such individual differences are currently recognized as critical traits that embody individuality [15-24] and its underlying biological mechanisms [25-28], and as an important variative material for evolution [23, 29-31]. Moreover, human disorders typically involve patient populations that are genetically and environmentally heterogenous, and cannot be standardized in a way as laboratory animals can [32, 33]. Combined with high heterogeneity of clinical behavioral symptoms [34, 35], and recent concerns over biological data replicability [36, 37], this collectively raises the question whether individual behavioral differences in animal models should be minimized or, instead, rigorously studied, especially since behavior of an individual is not the behavior of the average [38].

Common in various species, individual behavioral differences [39-44] are often affected by age, sex, size, social status and learned adaptive strategies [19, 45, 46]. However, it remains unclear whether this variability is due to consistent individual traits or random stochastic variation [47, 48]. Thus, further studies on individual traits and their variation are needed to examine this problem in depth. As already mentioned, one of such approaches involves varying animal environmental conditions [14][19333241, 29470495, 28448068], including environmental enrichment during neurobehavioral studies that minimizes risks of obtaining conflicting data in replicate studies [25000800,15602544, 19835063].

Another strategy in this field is to assess individual variance in a *wider* range of species, including rodents, primates, other mammals [49, 50] and aquatic (fish) organisms [51]. For example, the zebrafish (*Danio rerio*) is rapidly emerging as a new popular animal model for studying CNS disorders [52, 53]. This species not only possesses all the classical neurotransmitter systems of humans and neuropharmacological responses that parallel those in humans [54], but display high genetic and physiological homology to humans [55]. Together, this makes zebrafish a likely tool for preclinical research of individual behavioral traits and their variance [56]. Here, we evaluate mammalian and fish models to emphasize the importance of cross-species analyses of individual behavioral differences in experimental models of normal and pathological CNS processes.

As already mentioned, genetic and epigenetic factors play a key role in shaping behavioral strategies in human and animal populations [57-60]. In fact, animal personality variation attributable to additive genetic variation and heritability of personality is higher than heritability of behavior itself [61]. While some traits (e.g., bold/shy aggressiveness, aggressiveness, sociability and dominance/submission, Table 1) are generally conserved between species, other traits are species-specific (e.g., mammalian grooming and hissing or snail's protective withdrawal from shell). In humans, individual traits may also involve complex emotions (e.g., remorse, pride, shame and embarrassment) difficult to properly translate to animals and likely representing human-specific traits [62, 63]. Common methods of probing animal individuality experimentally

are based on exposing them to novel objects (e.g., shy-boldness tests) or conspecifics (e.g., aggression screens). Differences in boldness/shyness and aggression have been reported in various species, including rodents [64, 65], primates [66, 67], pumpkinseed sunfish [68] and zebrafish [69]. Animal shyness/boldness is context-specific and not always presents a unified behavioral trait [70], since individual differences that are adaptive in one context (e.g., predator defense) may not be adaptive in other contexts (e.g., exploration or social interactions) [71]. In fish, boldness can be assessed by various endpoints, including horizontal position, swim level, feeding latency [69], the latency to enter a novel environment, activity levels or reactions to threatening and benign novel objects [72].

Furthermore, much variance depends on the environment in which the animals live. For example, environmental enrichment can influence the results of different experimental protocols [73]. Thus, using enriched vs. standard conditions may help evaluate the impact of environmental enrichment. For example, mice exposed to an enriched environment attack intruders more frequently than controls kept in standard conditions [74]. Social enrichment also affects animal behavior. In rainbow trouts, bold fish reduce their boldness after observing losing conspecifics in fights [75]. Social isolation of rhesus monkeys triggers severe behavioral abnormalities that persist into adulthood, and animals with high impulsive aggression display lower brain serotonin [76]. Highly stereotypic (H) deer mice (*Peromyscus maniculatus bairdii*) group together in the presence of a non-stereotypic (N) conspecific, and are marginalized by animals of the N-cohort [77]. The sociability of deer mice is therefore modified by the level of stereotypy displayed by conspecifics, consistent with the social deficits in obsessive compulsive disorder (OCD) patients and their social experiences in the presence of healthy peers [78]. Social status affects access to food, mates and shelter and is associated with physiological profiles of the individuals and their health status [79, 80]. Many individual features (e.g., social dominance) can be at least partially heritable and expressed through the interaction between aggression-related epigenotypes, bringing genetic methods into studying individuality [69]. Thus, assessing common mechanism of how

individuality may be determined by internal (e.g., neurotransmitter or gene expression levels) or external factors may generate new insights into liability to mental diseases.

Behavioral individuality in mammalian and fish models

Albeit well-recognized [81, 82], the individual differences in rodent models continue to be actively studied. For example, individuals from the same laboratory vary in their motor and exploratory activity, and these differences are relatively consistent along the lifespan [83-85]. Levels of horizontal locomotor activity [84] or vertical rearing [86, 87] in response to novelty and performance in an exploration box [88] can assess variability of exploratory behavior [89]. Animal exploratory behavior is also linked to different pharmacological, environmental and age-related conditions, as, for example, is the case for amphetamine self-administration (higher in rodents with high exploration) and sensitization (weaker in high exploration) [83, 84], methamphetamine response (higher with high exploration) [90], memory impairment in old age (higher with high exploration) [85], anxiety- and depression-like behaviors (lower with high exploration) [91, 92], playfulness in early life (higher with low exploration) [93], neuroendocrine stress response [94], striatal dopaminergic activity [86] and basal dopamine levels in nucleus accumbens (all higher with high exploration) [95], and oxidative metabolism in dorsal raphe (lower with high exploration) [96].

Likewise, anxiety-like behavior can be measured by time spent in the open arm of the elevated plus-maze [97, 98], associated with avoidance behavior in the unconditioned burying test (lower with low anxiety) [8], playfulness in early life (higher with high anxiety) [93] and striatal serotonin levels (higher with low anxiety) [99]. Other paradigms to study rodent traits include testing extraversion, neuroticism [100], impulsivity and risk taking [101]. Overt individual differences can also be observed in the forced swim ‘despair’ test [102], cold-restraint stress [103], sucrose preference after chronic stress [104] and rapid acquisition tests [105]. Individual response to severe stress includes a continuum of high-to-low responders across a rodent population that parallels that observed in humans. Such naturalistic distribution of high risk vs. high resilience is particularly notable. Indeed, not all humans exposed to trauma will progress to full-blown post-

traumatic stress disorder (PTSD), with only 20-40% of victims developing the illness. Similar to 15–25% of trauma-exposed rodents presenting PTSD-like phenotypes [106, 107], this links differences in individual resilience profiles to the risk of developing PTSD.

Chronic exposure to stress hormones prenatally, during infancy, childhood, adolescence, adulthood or aging, impact the brain to ultimately preordain cognitive and mental illness. Their specific effects on brain and behavior are a function of the timing and the duration of the exposure, inter-twined with gene-environment influences [108, 109]. These aspects, modelled in animals using social isolation [110], maternal separation [111], chronic exposure to illicit drugs [112-114] or toxins [115, 116], offer invaluable preparations to study individual behavioral differences [110, 117].

Furthermore, rodents with specific traits can be selectively bred to reproduce these traits, such as apomorphine-susceptibility [118, 119] and locomotion in novel environment [120] (e.g., Mudsley reactive rats [121, 122] and Roman avoidance learning rats [123, 124]). Florida H (high anxiety) and L (low anxiety) rats that demonstrate two-fold difference in anxiety between H and L in males and three-fold difference in females [125]. Likewise, genetic analyses of individual traits have linked emotionality to three specific loci on chromosomes 1, 12 and 15 [126]. Moreover, the epigenetic transfer of behavioral traits has been shown in offspring of rats reared in social isolation [127] or following maternal separation [128].

As already noted, individuality occurs in genetically identical mice, including exploration, hippocampal neurogenesis [129], avoidance and risk assessment (e.g., the C57BL/6J mice displaying striking variation in learned fear) [130]. Individual features of aggressive behavior in different strains of rodents have also been identified, varying markedly in wild vs. laboratory animals (e.g., Wistar rats) [131]. WTG rats, for example, demonstrate varying aggression levels (from no to high) when an unfamiliar intruder male rat appears in their territory [132], whereas the variability of aggressive behavior is smaller in laboratory (e.g., Wistar rats) vs. wild-type animals [132]. However, in contrast to strain differences in intensity, the patterns of aggression in

domesticated rats do not differ from that of wild rats [133, 134], with similar 50-60% partial heritability [132].

However, rodent-based studies are insufficient for obtaining a whole picture of CNS pathogenesis, and multiple limitations impede translating rodent results into clinical practice. In contrast, nonhuman primates (e.g., rhesus macaques) are closer to humans in terms of physiology [76, 135, 136], behavior, social structure [137] and high (99%) genetic homology [138]. Due to the importance of these factors in studying nervous system and psychopathology, primates present with a major advantage over other animal models. Primate studies have revealed individual differences in addiction, flight-or-fight response, curiosity, aggressiveness and other behaviors [139-141]. For example, significant differences in social play, aggression and alcohol sensitivity between individuals are observed for different *rh5-HTTLPR* alleles, analogous to the human 5-*HTTLPR* polymorphism of the serotonin transporter *SLC6A4* gene [137].

Like other animal models, fish also exhibit overt individual behavioral differences [5, 56]. In Amazon molly (*Poecilia formosa*), individual behavioral differences can arise in clonal individuals raised in highly standardized conditions [142]. Different exploration strategies in novel object response and risk-taking behavior are seen in various isogenic lines of the rainbow trout (*Oncorhynchus mykiss*) [143]. In other fishes, differences in anxiety-like behavior are strain-dependent (e.g., higher in leopard and albino zebrafish) [144], whereas offspring activity levels in other species relies on social status and personality of parents [145]. Together, this emphasizes the role of both genetic and epigenetic components in behavioral individuality traits and its heritability mechanisms in fishes [142, 146]. However, while the two cloned red-spotted cherry salmon (*Oncorhynchus masou macrostomus*) strains show individual differences in boldness, activity and carefulness, variations in reactivity and greediness cannot be explained by differences between the clones [146]. Thus, individual differences may also arise from epigenetic or microenvironmental factors as well [142].

Spontaneous mutations can affect CNS morphological features and, hence, behavioral traits. For example, zebrafish epithalamus, especially the habenula, is involved in emotionality

and individual behavioral differences. The habenula is a key dorsal component conducting intermediate brain routes to connect the limbic sections of the forebrain, as well as the midbrain and posterior brain [147]. Interestingly, the habenula is asymmetrical in zebrafish [148]. Artificial selection for right-eye use when looking at own mirror image displayed a significant increase in frequency of reversed asymmetry in expression of *lov* gene in the habenula while selection for left-eye use tended to decrease it [149]. Thus, habenula development may be involved in the regulation of boldness in zebrafish, as mutations in the *lov* gene and subsequent aberrant asymmetry of habenula correlate with increased boldness [148]. Finally, various molecular mechanisms, including histone-related pathways, may underlie behavioral variability in fish, since laboratory and isogenic zebrafish larvae display consistent individual traits swimming freely or responding to experimental stimuli, but show reduced individual behavioral differences by disrupted histone deacetylation) [150].

Case in point: pain variability between humans, rodents, and fish

Pain is a complex physiological reaction to injury, directing nociceptive signals from pain receptors to the brain [151, 152]. In humans, genetic variance associated with variable pain phenotypes involves biogenic aminergic genes *GTP cyclohydrolase 1 (GCH1)*, *solute carrier family 6 member 4 (SLC6A4)*, *adrenoreceptor β -2 (ADRB2)* and serotonin 5-HT receptor 2A (*5-HTR2A*) [153], the vanilloid receptor subtype 1 (*TRPV1*), delta opioid receptor subtype 1 (*OPRD1*) and catechol O-methyltransferase gene (*COMT*) genes [154, 155]. There are also sex and ethnical differences in pain responses as women are more sensitive to cold and heat among all races, and Europeans of both sexes are more tolerant to cold, and Asians to hot, stimuli [156]. Furthermore, while neuropathic pain often evokes comorbid exhibit anxiety and depression [157, 158], severe anxiety increase pain sensitivity [159]. Depression-related pain can be also linked to neuroinflammatory or somatic mechanisms (e.g., microglial miscommunication) [160].

Complementing clinical studies, various rodent pain studies have focused on affective [161], cognitive [162], perceptual [163] and motor [164] components of pain responsivity using cold, heat, mechanical or chemical stimuli, inflammation and neuropathic pain models [165]. Like

humans, rodent pain responses show robust intraspecies variability. For example, rodent neuropathic pain evokes highly variable locomotor, social, anxiety-like and depression-like responses, with pain correlating with reduced sociability and increased anxiety and depression [162]. Pain-exposed rodents can also display social transfer of pain, inducing pain-like responses in intact animals [161, 166]. Likewise, genetic variance in rodents also contributes to variability in pain phenotypes. For example, mice lacking purinergic P2X4 receptors display reduced pain hypersensitivity to mechanical stimulus during inflammation and pain insensitivity in the spinal nerve injury model, but intact responses to thermal stimuli [167]. Cross-species analyses between humans and mice also reveal a critical role of testosterone in pain, as males from both species display reduced pain sensitivity under stress [168].

Relatively recently, pain has been studied in fishes. For example, the rainbow trout exhibits abnormal pectoral fin side-to-side movements and lip rubbing when given a noxious stimulus [169]. Juvenile Atlantic cods treated with capsaicin, acetic acid, or injured by fishing hook, displayed increased opercular beat rate, abnormal lateral head shaking, and frequent bottom hovering [170]. Zebrafish exposed to acetic acid exhibit characteristic abdominal constriction-like response and reduced locomotor activity [171]. While fish pain research is relatively young, some species differences are likely. For example, zebrafish do not alter the expression of nociception-related genes in dorsal root ganglia, one of the key structures in pain development [172], and also have different role of the nociceptin opioid receptor (NOP) that that of mammals [173].

Notably, there is an interesting nature of pain sensitivity cross-species stratification, modulated by inter-individual differences in neurophysiology, neurogenetics, neurochemistry and behavior [159]. In humans, variance in individual pain responses has long been reported [174], strongly implicating the endogenous opioid system [174, 175] (also see similar findings in rodents [176]). Like humans [177], rodents (e.g., C57Bl/6 mice) exhibit significant inter-individual variability in pain responses to thermal [178] or physical injury-related stimuli [179]. Supporting the role of genetic factors, such variance in pain responses is higher in outbred than inbred mice [180], and even genetically close inbred mouse sub-strains (e.g., C57BL/6J and C57BL/6NJ)

display distinct pain sensitivity responses to inflammatory and thermal stimuli [178]. Notably, the purinergic P2X4 receptors, essential in nociceptive responses, is also responsible for inter-individual pain variability in both humans and rodents [181]. Relatively little is known about zebrafish pain sensitivity variance, despite their generally conserved opioid system [182]. However, our own pilot data with several models of pain (Rosemberg and Costa, unpublished observations) support inter-individual difference in most pain indices in zebrafish, similarly to rodents and humans.

General discussion

Probing individuality in different animal species is promising for further translational behavioral research on learning, perception, memory and psychopathology [20]. However, most such studies are traditionally based on intra-species comparisons, even though some evolutionarily conserved behavioral traits or phenomena (e.g., locomotor activity, anxiety or fear/immobility) can be studied in more than one species, revealing a strong behavioral homology across phyla [183]. In human personality research, the distinction between intra- and cross-species comparison usually does not arise, because studies are performed on a single species (humans). Nevertheless, in the field of animal personality research, such distinction is important, and translational distortion should be taken into account.

Fishes, especially zebrafish, are rapidly becoming powerful animal model organisms for studying CNS disorders and behavior [52, 53]. For example, notable advantages of zebrafish include low cost, relatively simple neuronal organization and well-understood behavioral endpoints with diverse behavioral strategies and personal traits [15, 53, 184-186]. Specifically, sex variance can be observed in zebrafish studies on drug abuse, where males show more persistent drug-related [186] and novelty-evoked anxiety-like behaviors [187], as well as higher whole-body cortisol levels during chronic stress and aggression [185]. Likewise, stable strain-specific behavioral differences in zebrafish have also been reported [144].

In summary, animal models are highly suitable for studying personality development. Since it is a long-term process, longitudinal studies are needed to obtain the key data about markers

that can affect personality change. Animal lifespan is usually shorter than in humans, and such studies in animals take less time [188]. It is also easier to observe each day of an animal's life in laboratory conditions and manipulate these conditions to determine how they affect personality development during the lifespan. For example, confidence, excitability and sociability in a group of rhesus monkeys is associated with specific events in the animal's life (e.g., early separation from mother or colony) [189-191]. In contrast, longer lifetime, development periods, poorer control of the environment and ethical considerations make similar research complicated in humans.

Animal personality studies also enable genetic research that is cheaper than the equivalent humans studies and offers several important advantages [192, 193]. Indeed, behavioral genomics, focused on how genes and groups of interacting genes work to influence behavior, is at the center of such investigations [194]. With substantial molecular genetic research already done on mice [195], enough genomic information for this species is now available for gene-behavior research [194]. Together with gene mapping technologies [126, 196], it can help to reveal the complex basis of different behavioral traits. Knockout mouse models have developed into a significant tool to examine biological mechanisms hypothesized to underlie personality traits [197]. Transgenic methods and new cloning techniques could also be useful for animal research in genetic influence on personality [198, 199].

The availability of species with rich and complex social interactions enables research into interactions between different personality types, and how this may contribute to risk and resilience (e.g., see studies in the deer mouse [77]). Animal models also provide a valuable opportunity to experimentally test the effect of different stressors, for example, social, environmental or pharmacological, on personality development. In humans, personality has been linked to substance use and abuse [200, 201], academic performance [202], relationship outcomes and satisfaction [203, 204]. Thus, using animal models of different species (both human and non-human) is a promising option to understand human behavior and other CNS phenomena (Fig. 1). Furthermore, recent paradigms have shifted the focus from inherent and environmental factors to their complex

interactions [205]. For example, Gene-Environment interactions (GxE) show that different genotypes cause different individual sensitivity to an environmental factor, and that environment can indeed affect the CNS [206-212].

Despite criticism and fear to excessively anthropomorphize non-human personality, individuality and temperament, mounting evidence supports their existence in animals [20]. While there are obvious differences in methods of studying personality in human and animals, both fields now use personality traits as the core strategy to understand such differences in behavior [141]. Some traits (e.g., honesty, self-esteem and perfectionism) are difficult or impossible to access in species evolutionarily distant from humans, whereas other traits (e.g., activity, emotionality, bold/fear-like behavior, exploration or novelty seeking) are generally conserved and widely studied among species (Table 1), including primates, rodents and fish [20, 56]. However, because there is also a risk to ‘animal-morphise’ behavioral data (attributing animal motivations and behavioral characteristics to humans), critical evaluation of all behavioral traits become important. Recent progress in formalizing personality research by developing and applying its statistical definitions and models [213] may also foster research in this field. For example, as most statistical models assume that the study sample represents a random selection of individuals from the population, such studies may, in fact, target a specific behavior of the studied population that does not reflect the range of responses observed in nature, and neither applies to the population as a whole, nor targets the personality, individuality and temperament of individual responses [213].

Overall, the value of studying individual behavioral traits is unambiguous. As mentioned above, different individuals of the same species can display various responses to different stimuli despite sharing the same environmental conditions. For example, a significant difference exists for social games and aggressive behavior along with alcohol sensitivity between individual rhesus macaques with different *rh5-HTTLPR* alleles [137]. At the same time, zebrafish display robust sex differences, with males showing higher whole-body cortisol levels and more persistent drug-related anxiety behavior than females [214, 215]. Nevertheless, despite multiple studies of individual behavioral differences, many questions concerning the mechanisms underlying these

differences remain open (Table 2). For example, the exact biological nature of individuality and personality in behavior remains poorly understood (Fig. 1). Resulting from complex interactions involving a wide spectrum of factors, it is difficult to untangle and necessitate thorough control of inherent, intrinsic and environmental factors simultaneously. Thus, animal models represent a highly controllable tool that provides a powerful alternative in studies on personality and individual variation in behavior. This is made possible by the large amount of animal genetic data available, their short lifespan that helps observe development of personality easier and deeper compared to humans, and the absence of many ethic limitations, provides an important basis for their use as surrogate preparations to human studies.

Taken together, it underlines the significance and utility of animal models of different species in personality and individuality studies. For example, as shown in Fig. 1., cross-species analyses of putative shared behavioral traits and their variance may reveal evolutionarily conserved ‘shared’ biological mechanisms that underly both individual behavioral traits and their variance. In this case, intra-species variance may be simply explained by aberrant mechanisms that normally control and determine such behavioral traits per se. However, it is also possible that individual variance is at least partially mediated by unique, distinct molecular pathways unrelated to those of their respective traits. As such, focus on these putative novel mechanisms that specifically drive individual differences may be necessary. From this standpoint, cross-species studies that examine molecular mechanisms of intraspecies variance may be critical for revealing such shared (and, hence, evolutionarily conserved, ‘core’) mechanisms that specifically determine the variance of behavioral traits without directly affecting such traits per se (Fig. 1). Nevertheless, although using a wide spectrum of model species may be particularly beneficial for translational neuroscience research, including personalized neurology and psychiatry, special attention should be paid to ensuring adequate cross-species translation of such biological and behavioral data.

Finally, we also call for more innovation of research in this field, including a wider use of *novel* and underrepresented model organisms. For example, as discussed above, zebrafish emerge as one of such valuable model organisms for studying individual differences in behavioral traits

[refs], empowered by their highly conserved neurochemical systems and CNS drug targets with humans [53, 54, 216-218], drug screening potential [217, 218], high genetic homology to humans [55], external fertilization and the ease with which genetic manipulation can be performed [refs].

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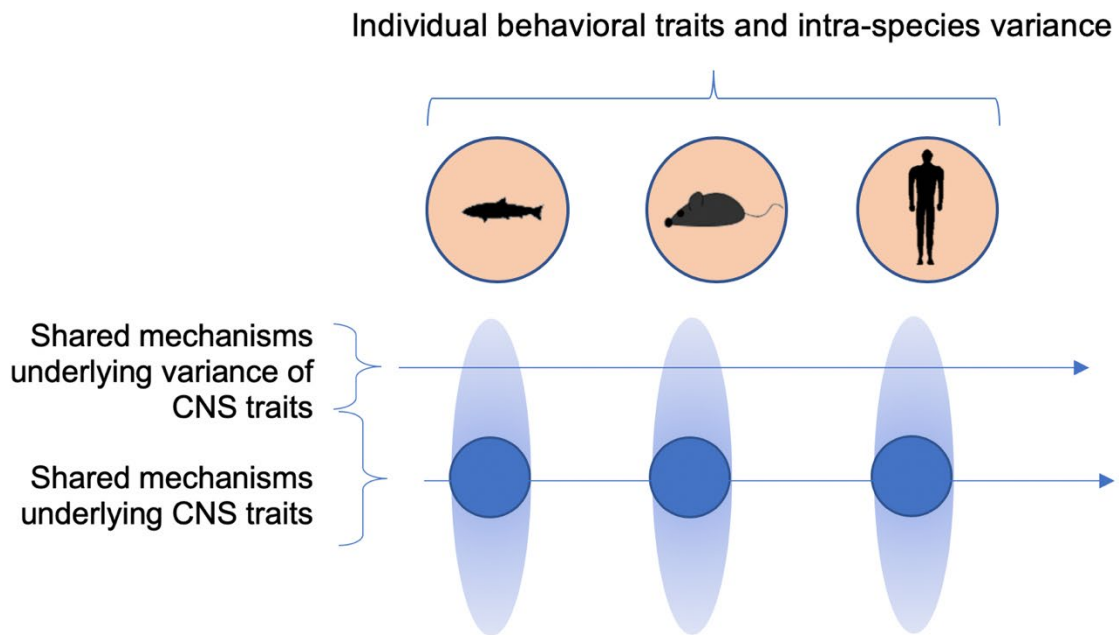
Table 1. Selected examples of individual behavioral traits across species.

Primates	Rodent	Fish
<p><i>Boldness</i> Heritability of personality in rhesus macaques and its association with fitness [140]; association between boldness and danger awareness in vervet monkeys [66]; distinct patterns of locomotor and boldness responses to novelty in cynomolgus monkeys [67]</p>	<p>Correlation between glucocorticoids and boldness in novel object responses [65]; safety/approach behaviors in an automated maze [219]</p>	<p>Overt bold-shy continuum (based on position in the tank and feeding latency) in zebrafish [69]; changes of boldness in the rainbow trout observing other fish lose fight [75]</p>
<p><i>Aggressiveness</i> Correlation of aggressive individual occurrence in rhesus monkeys with serotonin metabolism [136]</p>	<p>High aggression in Wildtype Groningen (WTG) rats [220]</p>	<p>Distinct aggressive behaviors (chase, bite, repel, spar) in zebrafish colonies [184]</p>
<p><i>Dominance</i> Fecal glucocorticoid metabolite correlates with social stress and dominance in Sichuan snub-nosed monkeys [221]</p>	<p>Heritability of social dominance traits [222]</p>	<p>Distinct patterns of plasma cortisol and telencephalic corticotrophin-releasing hormone, neuropeptide Y and glucocorticoid receptor gene expression in dominant vs subordinate fish [79]</p>
<p><i>Sociability</i> Peer-reared monkeys display extreme behavioral and physiological reactions to environmental challenges [76]</p>	<p>Social group size may promote the evolution of individual behavioral ‘signatures’, such as social alarm calls in sciurid rodents [80]</p>	<p>Social interaction affects growth, stress, immune function and reproductive condition [79]</p>

Table 2. Selected open questions to be clarified concerning the individual behavioral differences in animal models (also see Fig. 1) PLEASE RETURN ALL REMOVED/CROSSED GREEN QUESTIONS BACK TO THIS TABLE

- ~~• Are individual behavioral differences stable and determined by specific biological mechanisms, or they are generally more random and stochastic?~~
- While many factors (e.g., environment and genetics) can contribute to individual behavioral differences, what are common neurological mechanisms resulting in stability of certain behaviors?
- Are putative biological mechanisms driving individual behavioral variance merely the result of inactivity of molecular pathways controlling the stability of behavioral traits, or they represent distinct molecular machinery?
- How similar are individual behavioral characteristics in mammals (including primates) and zebrafish?
- How evolutionarily ancient are various complex behavioral traits, such as emotionality (e.g., ~~can they were observed in C. elegans [223]~~)?
- Can more complex patterns and traits (e.g., honesty, self-esteem, perfectionism, etc.) be observed in animal models, including model organisms?
- How can these complex patterns be modulated pharmacologically, genetically or epigenetically?
- Are there any strong epigenetic markers of particular individual behavioral patterns?
- How differently can stress modulate behavioral patterns in individuals of one group/population?
- How can individual behavioral traits (and their variance) in animal models be used as biomarkers for CNS disorders of humans?
- How can individual behavioral traits in animal models be used for developing personalized psychiatry for humans?
- How can behavioral variation be modified environmentally (e.g., environmental enrichment), especially in novel model organisms (e.g., zebrafish)?
- ~~• Can animals react in an opposite (to the original trait) manner depending on their environment?~~
- How can individual traits be reversed/relearned?
- How can individual differences of the experimenters contribute to an animal individual differences observed in a study?
- Can there be separate groups of genes modulating variance of individual traits (Fig. 1) without affecting the traits per se?

Figure 1. Cross-species analyses of putative shared behavioral traits and their variance may reveal overlapping, evolutionarily conserved biological mechanisms underlying both individual behavioral traits and their variance. For example, intra-species variance may arise from aberrant mechanisms that normally control and determine such behavioral traits. However, it is also possible that individual variance is at least partially mediated by distinct molecular pathways unrelated to those of their respective traits per se. As such, focus on these putative novel mechanisms that specifically drive individual differences may be necessary. From this standpoint, cross-species studies that examine such unique molecular mechanisms of intraspecies variance may also be critical, helping to identify shared (and, hence, evolutionarily conserved, ‘core’) mechanisms that specifically and solely determine the variance of behavioral traits (also see Table 2).



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