Available online at www.sciencedirect.com

SCIENCE DIRECT®

Brain Research Reviews 48 (2005) 1–15

BRAIN RESEARCH REVIEWS

www.elsevier.com/locate/brainresrev

Review

Behavioral correlates of differences in neural metabolic capacity

Jon T. Sakata[a], David Crews[a], F. Gonzalez-Lima[a,b,*]

[a]*Institute for Neuroscience, University of Texas at Austin, Austin, TX 78712, United States*
[b]*Department of Psychology, University of Texas at Austin, Austin, TX 78712, United States*

Accepted 26 July 2004
Available online 1 September 2004

Abstract

Cytochrome oxidase is a rate-limiting enzyme in oxidative phosphorylation, the major energy-synthesizing pathway used by the central nervous system, and cytochrome oxidase histochemistry has been extensively utilized to map changes in neural metabolism following experimental manipulations. However, the value of cytochrome oxidase activity in predicting behavior has not been analyzed. We argue that this endeavor is important because genetic composition and embryonic environment can engender differences in baseline neural metabolism in pertinent neural circuits, and these differences could represent differences in the degree to which specific behaviors are 'primed.' Here we review our studies in which differences in cytochrome oxidase activity and in behavior were studied in parallel. Using mammalian and reptilian models, we find that embryonic experiences that shape the propensity to display social behaviors also affect cytochrome oxidase activity in limbic brain areas, and elevated cytochrome oxidase activity in preoptic, hypothalamic, and amygdaloid nuclei correlates with heightened aggressive and sexual tendencies. Selective breeding regimes were used to create rodent genetic lines that differ in their susceptibility to display learned helplessness and in behavioral excitability. Differences in cytochrome oxidase activity in areas like the paraventricular hypothalamus, frontal cortex, habenula, septum, and hippocampus correlate with differences in susceptibility to display learned helplessness, and differences in activity in the dentate gyrus and perirhinal and posterior parietal cortex correlate with differences in hyperactivity. Thus, genetic and embryonic manipulations that engender specific behavioral differences produce specific neurometabolic profiles. We propose that knowledge of neurometabolic differences can yield valuable predictions about behavioral phenotype in other systems.

Topic: Neural basis of behavior
Theme: Neural plasticity

Keywords: Cytochrome oxidase; Individual differences; Sexual differentiation; Aggression; Courtship behavior; Depression; Learned helplessness; Hyperactivity; Attention deficit

Contents

* Corresponding author. Department of Psychology, 1 University Station A8000, University of Texas at Austin, Austin, TX 78712-0187, United States. Tel.: +1 415 502 3279; fax: +1 415 476 4929.
E-mail address: gonzalez-lima@psy.utexas.edu (F. Gonzalez-Lima).

0165-0173/$ - see front matter © 2004 Elsevier B.V. All right reserved.
doi:10.1016/j.brainresrev.2004.07.017

1. Introduction

Neural activity is the basis of all behaviors. All sensory stimuli impinging on the individual are translated into neural activity, and neural activity governs our actions and understanding of our surroundings. It is not surprising, therefore, that a fundamental parameter of interest in neuroscience is the activity of single neurons or populations of neurons. How neurons in different brain areas respond to different exogenous stimuli and code for different behaviors, and how activity in pertinent brain areas underlie learning and memory are questions of great interest and major importance. Documenting and understanding the plasticity of the brain, or more specifically how the encoding of different stimuli or behaviors changes as a function of experience, and the constraints to this plasticity have significant implications for medicine, psychology, and physiology.

Neural activity is constrained, in part, by the availability of cellular energy, primarily ATP. Furthermore, the production of ATP is constrained by pertinent enzymes involved in oxidative phosphorylation, the major energy-synthesizing pathway utilized by the central nervous system [35,36]. The enzyme, cytochrome oxidase (cytochrome *aa*3 or ferrocytochrome *c*), is a terminal enzyme of the electron transport chain (complex IV) located in the inner mitochondrial membrane, and it catalyzes the transfer of electrons to oxygen to form water and ATP; thus, cytochrome oxidase is a rate-limiting enzyme in oxidative phosphorylation [139]. In this respect, the activity of cytochrome oxidase determines the amount of ATP available in a neuron, which could constrain the amount of activity that a neuron can sustain. Therefore, cytochrome oxidase activity can serve as a marker of metabolic capacity that could be correlated to behavior [41].

Wong-Riley et al. [146] have elegantly documented the series of molecular events and parameters regulating cytochrome oxidase expression and activity. Cytochrome oxidase is a holoenzyme composed of 13 proteins, 10 of which are encoded in the nuclear genome and three of which are encoded in the mitochondrial genome [54,55,146,152]. The catalytic subunits seem to be encoded in the mitochondrial genome because transcription of mitochondria-encoded cytochrome oxidase genes correlates better with cytochrome oxidase activity than nuclear-encoded cytochrome oxidase genes (Refs. [55,89]; but see Ref.[73]). Cytochrome oxidase activity is determined primarily by the abundance of the holoenzyme in the mitochondria [52,55]. Therefore, cytochrome oxidase activity is governed by a complex interaction between intracellular factors that affect both nuclear and mitochondrial gene expressions. For example, GA-binding protein and nuclear respiratory factors 1 and 2 are important in the transcription of cytochrome oxidase genes, and levels of expression of these transcription factors correlate with cytochrome oxidase [91,149,153].

The abundance and activity of cytochrome oxidase are tightly linked to the energy demand involved in neuronal activity and to the ratio of excitatory/inhibitory inputs. Changes in cytochrome oxidase are not limited to particular neurotransmitters or cell signaling systems. Instead, changes in cytochrome oxidase activity closely follow those of the Na^+/K^+ pump, which restores the resting membrane potential in excitable cells such as neurons because this pump demands the highest amount of ATP in neurons [56,60,61,146–148]. For example, experimentally induced decreases in afferent excitatory input (e.g., via tetrodotoxin) lead to significant decrements in cytochrome oxidase activity [28,53,55,56,62,84,89,91,140–145,147,148,151,152].

In general, increased excitatory input and decreased inhibitory input are correlated with increased cytochrome oxidase activity [72,83,88,90,151]. For example, in the supragranular layers of the macaque extrastriate cortex, cytochrome oxidase-rich zones have more glutamate-immunoreactive synapses relative to cytochrome oxidase-poor zones [90], and NMDAR1 expression is positively correlated with cytochrome oxidase activity in cortical neuronal cultures [151].

Because cytochrome oxidase is intimately linked to neuronal activity, cytochrome oxidase histochemistry has traditionally been used to assess the metabolic history of an area (e.g., Refs. [9,53,140]). In this respect, cytochrome oxidase has been used to trace functional pathways activated during a series of experiences. Information on cytochrome oxidase activity is very different from information based on other metabolic markers such as 2-deoxyglucose and immediate early genes such as c-*fos*; the latter markers provide information on evoked or immediate activity, whereas cytochrome oxidase activity reflects long-term changes in brain activity [41]. For example, 2-deoxyglucose consumption during training or learning tasks reflects ongoing metabolic changes that occur during learning, while changes in cytochrome oxidase activity after learning reflect long-term changes in neural metabolic capacity as a consequence of learning [98]. The activity of cytochrome oxidase is more stable over time relative to 2-deoxyglucose uptake or c-*fos* expression and reflects

neural activity that has accumulated over hours to days, rather than minutes [41,57]. Moreover, cytochrome oxidase histochemistry has increased anatomical resolution relative to 2-deoxyglucose autoradiography, and, unlike cellular metabolic markers such as c-*fos* and other immediate early genes, cytochrome oxidase activity is less dependent on specific intracellular signaling mechanisms [42,94].

Despite the large number of studies documenting the effects of particular experiences on neural activity (thereby identifying functional neuronal circuits), there is a paucity of studies highlighting the behavioral correlates of baseline differences in cytochrome oxidase activity caused by embryonic or genetic influences. In other words, there are few studies that relate endogenous differences in cytochrome oxidase activity to differences in behavioral phenotype. We propose that differences in cytochrome oxidase activity in pertinent neural circuits could relate to differences in specific behavioral propensities. For example, it is plausible that particular individuals display more aggressive behavior than others because baseline metabolic activity and, consequently, cytochrome oxidase activity are elevated in areas underlying agonistic behavior. Difference in the amount of excitatory and inhibitory inputs, which leads to differences in cytochrome oxidase activity, in brain areas underlying agonistic behavior could also lead to variation in the propensity to display aggressive behavior. These metabolic differences may result from genetic or embryonic influences on neural populations. The analysis of neural metabolism in naïve individuals provides a potential window into biological factors contributing to individual differences in behavioral propensities.

Here, we review our recent studies highlighting the predictive information of differences in cytochrome oxidase activity. By running parallel neurobiological and behavioral experiments, we correlate group differences in neural metabolic phenotype in pertinent brain areas with behavioral differences across groups. We review our recent work on both rodent and lizard species to provide a comparative framework for understanding individual differences, and we analyze the relationship between cytochrome oxidase activity and differences in the expression of social behaviors, helplessness, and behavioral excitability. An understanding of species similarities as well as differences is fundamental for generating predictions on brain–behavior relationships in other species including humans. We organize our review based on behavioral phenotype and processes instead of species to emphasize the comparative aspect of our work.

2. Cytochrome oxidase activity and differences in the propensity to display sexual and aggressive behaviors

Sexual differentiation refers to the feminization and masculinization of phenotype. In many vertebrate species, the process of sexual differentiation centers on the perinatal period, and gonadal sex steroid hormones are primary agents in this process. For example, androgenic and estrogenic stimulation perinatally leads to the behavioral and neural masculinization in adulthood (see Refs. [19,96]).

It has long been known that the intrauterine environment can have lasting effects on physiology and behavior. For example, the position of the rodent embryo in the uterine horn affects the amount of exposure to prenatal androgens: embryos situated between two male fetuses (2M embryos) are exposed to more androgens than embryos situated between two female fetuses (2F embryos) [18,134,135]. This difference in androgen exposure causes dramatic behavioral variation in adulthood (reviewed in Refs. [16,105]). For example, relative to 2F female gerbils, 2M females are more likely to display male-typical mounting behavior toward females following testosterone administration. Further, 2M females have fewer litters and reproduce at a later age [15,17].

Jones et al. [59] investigated differences in cytochrome oxidase activity in limbic brain areas between 2M and 2F female gerbils. When comparing the ratio of cytochrome oxidase activity in gray matter to white matter, 2M female gerbils have elevated cytochrome oxidase reactivity in the medial and posterior anterior hypothalamic areas relative to 2F females. These areas of the anterior hypothalamus are sexually dimorphic and are involved in steroidogenesis [138,150]. No differences in the medial preoptic area, paraventricular hypothalamus, or ventromedial hypothalamus were found—areas that have been implicated in the regulation of sociosexual behaviors in other mammalian species [81]. These data suggest that heightened metabolic activity in the anterior hypothalamus is correlated with a heightened propensity to display heterotypical mounting behavior in response to testosterone treatment.

In many reptilian species, gonadal sex is determined not by sex chromosomes but by the incubation temperature experienced by the embryo during development (i.e., temperature-dependent sex determination), and one such lizard is the leopard gecko, *Eublepharis macularius* [130] (Table 1). Only females are produced at the extreme incubation temperatures, whereas mixed sex ratios are produced at intermediate incubation temperatures. Interestingly, in this species, incubation temperature not only determines gonadal sex but also has profound effects on reproductive physiology and behavior that parallel intra-

Table 1
Sex ratios as a function of incubation temperature in the leopard gecko

Incubation temperature (°C)	Sex ratio (% male)	Label
26	0	Low
30	~30	Female-biased
32.5	~70	Male-biased
34	<5	High

uterine position effects (reviewed in Refs. [24,110]). As in other species, male leopard geckos, regardless of incubation temperature, have elevated androgen and lower estradiol concentrations than females, and are more likely to display aggressive, territorial, and courtship behavior. However, when comparing socially naïve adults, the phenotype of individuals from different incubation temperatures varies dramatically. For example, males and females hatched from eggs incubated at warmer incubation temperatures are more aggressive toward intruders than their same-sex counterparts hatched from eggs incubated at cooler incubation temperatures [39]. Adult male leopard geckos from an incubation temperature that produces predominantly males (32.5 °C, or male-biased incubation temperature) have lower estradiol concentrations relative to adult males from an incubation temperature that produces a female-biased sex ratio (30 °C, or female-biased incubation temperature) [20,127]. Across the reproductive cycle, females from the high incubation temperature have elevated circulating concentrations of androgens relative to females from the low and female-biased incubation temperatures [102]. Many behavioral differences in the leopard gecko persist following gonadectomy and equalization of hormone concentrations, suggesting that endocrine differences caused by incubation temperature and gonadal sex are not paramount in producing behavioral differences [22,38,100]. For example, differences in territorial behavior between males from the female- and male-biased incubation temperatures persist following castration and identical androgen treatment [100], and differences in courtship behavior between males and females persist following identical androgen treatments [100].

It is important to emphasize that these behavioral tests were administered to socially naïve animals; therefore, these differences reflect differences in the predisposition to display different social behaviors. All individuals were raised in individual cages from hatching, although visual and olfactory communication was available. A great benefit in studying reptiles like leopard geckos is that, aside from genes and maternal contribution to the yolk, neither parent contributes to the development of the individual. Therefore, confounding factors such as anogenital grooming in rodents, which is differentially administered across the sexes (e.g., male rat pups receive more anogenital grooming) and influential in the masculinization of the individual [85], do not exist in these lizard species.

Coomber et al. [20] analyzed between-sex (within incubation temperature) and within-sex (across incubation temperature) differences in cytochrome oxidase activity in limbic brain areas of naïve geckos. Sex differences were investigated primarily among individuals from the female- and male-biased incubation temperatures. Only 3 of 16 nuclei examined show consistent sex differences at both the female- and male-biased incubation temperatures. Namely, at both incubation temperatures, males have greater cytochrome oxidase activity in the nucleus sphericus, an amygdaloid nucleus that receives projections from the accessory olfactory bulb [48], whereas females have higher cytochrome oxidase activity in the dorsolateral hypothalamus and ventromedial hypothalamus (Fig. 1). The latter finding is consistent with the notion that the ventromedial hypothalamus is an evolutionarily conserved brain area involved in the display of female-typical reproductive behaviors [21]. Therefore, when examining sex differences, heightened aggressiveness and copulatory behavior are correlated with elevated cytochrome oxidase activity in the nucleus sphericus, and heightened expression of receptive behavior is associated with higher cytochrome oxidase activity in the dorsolateral and ventromedial hypothalamic nuclei.

Parallels between behavioral differences and neurometabolic differences are also found when analyzing within-sex variation. In females, aggressiveness toward males is highest in females from the male-biased and high incubation temperatures, moderate in females from the female-biased incubation temperature, and lowest in females from the low incubation temperature [39]. When analyzing intrasexual neurometabolic differences among females from the four incubation temperatures, it is most common to find that females from the male-biased incubation temperature have the highest cytochrome oxidase activity (e.g., anterior hypothalamus, external nucleus of the amygdala, nucleus sphericus, preoptic area, and septum). Only in the ventromedial hypothalamus do females from the female-biased incubation temperature have the highest cytochrome oxidase activity. The pattern of neural metabolic differences among females in the external nucleus of the amygdala best matches the pattern of differences in aggressiveness, suggesting that heightened baseline activity in this nucleus could predispose females to attack males (Fig. 2). The external nucleus of the amygdala has been implicated in the display of agonistic

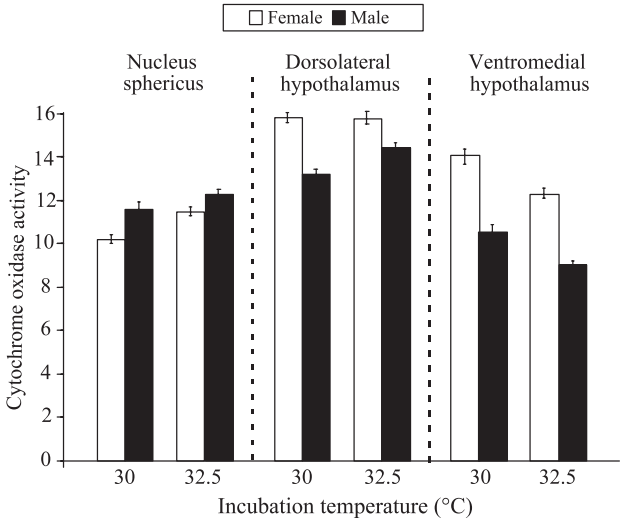

Fig. 1. Consistent sex differences in cytochrome oxidase activity (μmol/min/g tissue wet weight) between males and females from both the female-biased (30 °C) and male-biased (32.5 °C) incubation temperatures. For all sex differences, $p<0.01$ [20].

behavior in other reptiles [47,126] and expresses high levels of androgen receptor mRNA [101]. Interestingly, testosterone treatment of ovariectomized females from low incubation temperature increases both aggressiveness toward males and cytochrome oxidase activity in the external nucleus of the amygdala [22]. Because the ventromedial hypothalamus is an evolutionarily conserved brain area controlling the display of female-typical sexual, it is possible that the differences in cytochrome oxidase activity in this area caused by incubation temperature could lead to variation in the expression of receptive behaviors. However, we have yet to adequately examine whether incubation temperature affects receptive behavior in females (but see Refs. [100,102]).

Females from the male-biased temperature are more likely to display male-typical courtship behaviors following testosterone treatment relative to females from the low incubation temperature [22]. Intact females from the male-biased incubation temperature have elevated cytochrome oxidase activity in areas such as the anterior hypothalamus, external nucleus of the amygdala, nucleus sphericus, septum, and preoptic area relative to females from the low incubation temperature [20]. Therefore, elevated metabolic capacity in these areas could prime the display of courtship behavior following testosterone administration, and preoptic, hypothalamic, and amygdaloid nuclei are likely candidates. A similar correlation between elevated cytochrome oxidase activity in the anterior hypothalamus and a heightened propensity to display male-typical sexual behavior was found in female gerbils [59].

Incubation temperature-dependent behavioral variation among males is similar to that among females, as are neurometabolic correlates. Males from the male-biased incubation temperature are more aggressive and territorial than males from the female-biased incubation temperature, even when controlling for gonadal steroid concentrations [39,100]. Males from the male-biased incubation temperature have elevated cytochrome oxidase activity in the anterior hypothalamus, nucleus sphericus, and septum relative to males from the female-biased incubation temperature. Therefore, just as in females, elevated metabolic capacity in the anterior hypothalamus, nucleus sphericus, and septum is correlated with heightened aggressiveness and territoriality, and this is consistent with the modulatory role of hypothalamic, amygdaloid, and septal nuclei in agonistic behavior in other species [2,26,45,67,81,114]. On the other hand, unlike females, no difference in the external nucleus of the amygdala exists between males from the female- and male-biased incubation temperatures, which suggests that there could be variation in the mechanism underlying intrasexual variation in agonistic behavior among males and among females.

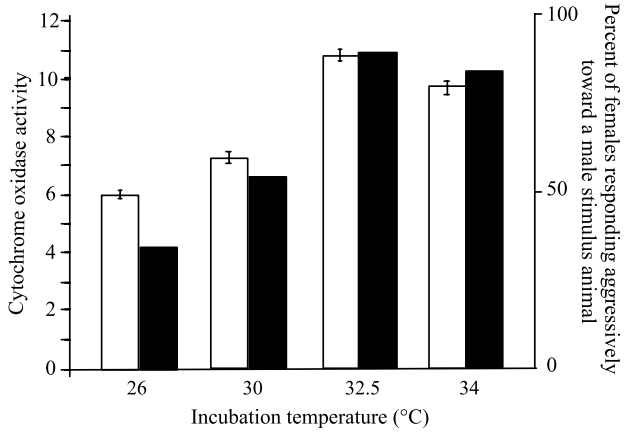

Fig. 2. Relationship between cytochrome oxidase activity in the external nucleus of the amygdala and propensity to attack male stimulus animals in female leopard geckos. Empty bars represent cytochrome oxidase activity (μmol/min/g tissue wet weight) [20], whereas filled bars represent the percent of females that responded aggressively toward males [39]. Differences in cytochrome oxidase activity among all groups are significant ($p<0.01$) [20], and the difference in the percent of females attacking male intruders is significant between females from the low incubation temperature and females from both the male-biased and high incubation temperatures ($p<0.05$) [39].

Furthermore, whereas females from the male-biased incubation temperature have higher cytochrome oxidase activity in the preoptic area relative to females from the female-biased incubation temperature, males from the female-biased incubation temperature have elevated metabolic capacity in the preoptic area relative to males from the male-biased incubation temperature. Interestingly, intrasexual behavioral differences also vary between males and females. Whereas females from the male-biased incubation temperature are the most likely to display male-typical courtship behavior following androgen administration, males from the female-biased temperature show more courtship and copulatory behavior when intact, following castration, and following androgen treatment relative to males from the male-biased incubation temperature [100,111]. What is similar across the sexes is that elevated metabolic capacity in the preoptic area is correlated with a heightened propensity to display courtship behavior. This is consistent with the evolutionarily conserved role of the preoptic area in the display of male-typical sexual behavior [21,81] and suggests that elevated preoptic area metabolism could prime the display of courtship behavior in males and females [110,111]. Males from the female-biased temperature are also more likely to show signs of sexual conditioning and increased territorial behavior following repeated copulatory interactions with females [109]. Because the preoptic area has also been implicated in conditioned sexual arousal [97,103], heightened preoptic area metabolism might also facilitate experience-dependent changes following social interactions.

It will be important to assess the effects of developmental factors on glutamatergic innervation in mammals such as gerbils and in reptiles given the effects on cytochrome oxidase activity in limbic brain regions and given the relationship between cytochrome oxidase activity and glutamatergic innervation. There exists evidence that perinatal sex steroid hormone exposure affects excitatory transmission in hypothalamic brain regions [25,79]. Given

that experience-dependent changes in social behavior are affected by NMDA receptors in male rats [7,99] and that differences in metabolic capacity in the preoptic area correlate with incubation temperature-dependent differences in behavioral plasticity following sociosexual experiences in male leopard geckos, it is plausible that incubation temperature affects NMDA receptor expression in the preoptic area in male leopard geckos. Glutamatergic innervation is important for the expression of copulatory behavior [99,123], and, consequently, variation in the propensity to display sexual behavior caused by developmental factors could be related to changes in the glutamatergic system and, consequently, cytochrome oxidase activity.

3. Differences in cytochrome oxidase activity and the predisposition for learned helplessness

Using a learned helplessness paradigm, Henn and Edwards [51] selectively bred together rats that were vulnerable to displaying learned helplessness following inescapable shock as well as rats that were resistant to learned helplessness. In brief, rats were first exposed to mild inescapable shocks [34]. Twenty-four hours later, they were tested in a situation in which shocks could be prevented by a single bar press. Some animals successfully learned to terminate the controllable stress, whereas others failed to acquire this response, and males and females within each group were selectively bred together. This breeding program was very successful in generating both susceptible and resistant individuals. For example, whereas 20% of normally outbred rats are vulnerable to learned helplessness using their shock paradigm, up to 95% of selectively bred susceptible rats show this phenotype [51]. The genetic susceptibility to helplessness increased with selective breeding until a steady state was reached after 25 generations, when 95% of the susceptible rats started showing spontaneous helpless behavior in the absence of any training or stress [68]. Thus, the congenitally helpless rat line shows a helpless phenotype resembling depressions that appear spontaneously, without stressful events. This allows the investigation of neural differences related to a depressive phenotype because innate differences can be observed in naïve rats of the congenitally helpless line independently from any stress manipulations.

Shumake et al. [119–122] have investigated differences in cytochrome oxidase activity in cortical and subcortical brain areas between two genetic lines of selectively bred Sprague–Dawley rats (Table 2). Since our objective was to examine the neurometabolic predisposition to develop helpless behavior—not the brain's evoked response to stress—cytochrome oxidase histochemistry has provided a unique way to isolate this component by identifying the brain regions affected in the congenitally helpless male rats. As extensively reviewed by Shumake and Gonzalez-Lima [118] and briefly explained below, affected regions include brain areas regulating the hypothalamic–pituitary–adrenal axis, prefrontal cortical areas affected in depressed humans, and regions mediating psychomotor retardation and anhedonia.

Table 2
Regions with altered metabolic activity in congenitally helpless male rats relative to nonhelpless male rats

Helpless < nonhelpless	Dorsal prefrontal cortex
	Medial orbital cortex
	Anterior cingulate cortex
	Basolateral and central amygdaloid nuclei
	Lateral septal nucleus
	Bed nucleus of the stria terminalis
	Caudate–putamen
	Nucleus accumbens
	Ventral tegmental area
Helpless > nonhelpless	Infralimbic cortex
	Hippocampus (CA1 and CA3)
	Subiculum
	Paraventricular hypothalamic nucleus
	Habenula
	Interpeduncular nucleus

The largest metabolic difference (80%) between the congenitally helpless and nonhelpless rats occurs in the paraventricular hypothalamus, a brain region regulating the hypothalamic–pituitary–adrenal axis that mediates the physiological responses to stress, and congenitally helpless rats have higher cytochrome oxidase activity in this area. This paraventricular hypothalamus difference is the largest cytochrome oxidase baseline difference encountered in any of our studies with intact rodents. Given that stress activates the paraventricular hypothalamus [92] and that chronic stress can lead to depression, it follows that the paraventricular hypothalamus may become hyperactive in stress-induced depression. What is interesting about the congenitally helpless rats is that they show paraventricular hypothalamus hypermetabolism without any environmental stressor, suggesting that paraventricular hypothalamus hyperactivity can also be caused by genetic selection. These findings suggest a new theory that combines the contributions of heredity and stress in the etiology of depression: if sustained hyperactivity of the paraventricular hypothalamus leads to depression, then individuals with higher baseline metabolic capacity in the paraventricular hypothalamus would be more prone to develop depressed phenotypes [118].

Relative to nonhelpless rats, naïve congenitally helpless rats show decreased metabolism in the dorsal frontal, medial orbital, and anterior cingulate cortical areas but increased cytochrome oxidase activity in the infraradiata cingulate cortex. Additionally, congenitally helpless rats have elevated metabolic capacity in the hippocampus, subiculum, habenula, and interpeduncular nucleus and reduced cytochrome oxidase activity in the septum, nucleus of the diagonal band, bed nucleus of the stria terminalis, basolateral and central amygdala, ventral tegmental area, and basal ganglia. Elevated metabolic activity in the habenula and lower metabolic activity in the dorsal medial prefrontal

cortex have also been found in rats showing depressed phenotypes using ^{14}C-2-deoxyglucose autoradiography [11]. Increased cytochrome oxidase activity in the hippocampus of congenitally helpless rats is consistent with increased glutamate activity and decreased GABA activity in the hippocampus of learned helpless rats [95]. The reduced cytochrome oxidase activity in the septum is correlated with a reduced activation of the lateral septum following stressors [124], and this could inhibit the acquisition of behaviors to avoid or terminate stressors. Decreased metabolic capacity in the basolateral and central amygdaloid nuclei in congenitally helpless rats is consistent with studies implicating the amygdala in escape learning [37,76,86], aversive conditioning, stress [124,136], and anxiety [107,108,117]. Deficits in escape learning could be due to the inability of stressful situations to sufficiently activate neurons in the basolateral and central amygdala that contribute to acquiring an escape response. Further, the amygdala hypometabolism in helpless rats is consistent with the notion that congenitally helpless rats have less dopaminergic innervation from the ventral tegmental area [122], and we interpret this as reflecting an impaired reward system [118].

Interestingly, these patterns of change in congenitally helpless rats resemble the neurometabolic phenotype of depressed humans [118]. For example, the reduced metabolic capacity in the dorsal frontal and anterior cingulate cortices and in the basal ganglia of congenitally helpless rats is reminiscent of the reduced metabolism in the dorsolateral prefrontal, supragenual anterior cingulate, and basal ganglia in depressed patients [30,104]. Increased metabolic capacity in the hippocampus of congenitally helpless rats is consistent with human neuroimaging data showing a reduction in hippocampal activity after treatment with antidepressants [78]. However, in areas like the pregenual cingulate, lateral orbital, and anterior insular cortices in which metabolic differences have been found in depressed individuals, no differences in metabolic capacity were found in the homologous brain regions in these rats.

Increased cerebral blood flow to the amygdala has been reported in depressed humans, and depression severity positively correlates with baseline metabolic activity in the amygdala (reviewed in Refs. [30,32]). Further, treatment with antidepressants leads to a decrement in amygdaloid activity [31]. Because of the relationship between baseline metabolic activity and cytochrome oxidase activity, Shumake et al. [122] anticipated that congenitally learned helpless rats would have elevated cytochrome oxidase activity in amygdaloid nuclei but found the opposite pattern of results (Table 2). Although this is inconsistent with previously mentioned human studies, these data are consistent with Kimbrell et al. [64], who report decreased metabolism in anterior paralimbic regions of depressed patients, around and encompassing some of the amygdala. Abercrombie et al. [1] report that in other patients meeting the criteria for major depressive disorder, right amygdala metabolism predicted negative affect, but neither left nor right amygdala metabolism predicted depression severity or differentiated depressives from control. Human studies also show that amphetamine and cocaine administration increases blood flow to the amygdala [27], and cocaine withdrawal, which mimics many symptoms of depression, is accompanied by amygdala hypometabolism in rats [50]. Furthermore, despite the relationship between elevated activity in the left amygdala in humans and depression [30–32], elevations in left amygdaloid activity have been found following exposure to arousing sexual stimuli [49], suggesting that the functional significance of activity in the left amygdala is complex.

Neurometabolic differences between congenitally helpless and nonhelpless male rats might not only reflect differences in the predisposition for learned helplessness or deficits in escape learning but could also reflect other behavioral differences related to a depressive phenotype. For example, congenitally helpless rats show reduced dominance and sex drive and loss of appetite and weight. There is reduced cytochrome oxidase activity in areas implicated in aggression and sexual behavior such as the septum, bed nucleus of the stria terminalis, and ventral tegmental area [58,81]. Similarly, less aggressive leopard geckos have reduced cytochrome oxidase activity in the septum [20]. Interestingly, despite the reduced sex drive in congenitally helpless rats, metabolic capacity in the preoptic area and medial amygdala is not significantly different between congenitally helpless and nonhelpless male rats. This suggests that the mechanisms underlying differences in copulatory propensities caused by embryonic influences in leopard geckos (see above) could be different from that caused by selective breeding of the helpless phenotype in rats. Alternatively, this could represent species differences in the relationship between neural metabolism and behavioral propensities. There is support for the latter hypothesis in that cytochrome oxidase activities in the preoptic area and amygdala are not different between sexually vigorous and sluggish Sprague–Dawley male rats [113].

It should be mentioned that neural differences between congenitally helpless and nonhelpless rats could be due to changes in congenitally helpless rats, in nonhelpless rats, or in both. For example, the fact that congenitally helpless rats have elevated neural activity in the paraventricular hypothalamus relative to nonhelpless rats could mean that congenitally helpless rats have high cytochrome oxidase activity, that nonhelpless rats have low cytochrome oxidase activity, or both. Cytochrome oxidase activity in the paraventricular hypothalamus of Sprague–Dawley rats not selectively bred for any purpose is intermediate between congenitally helpless and nonhelpless rats, suggesting that congenitally helpless rats have high cytochrome oxidase activity and nonhelpless rats have low cytochrome oxidase activity [120]. The driving force underlying other differences in cytochrome oxidase activity appears to be similar, but further research is needed.

4. Differences in cytochrome oxidase activity in a model of hyperactivity and attention deficit

The neurometabolic basis of the genetic predisposition for hyperactivity and attention deficit has been investigated using cytochrome oxidase histochemistry in male Naples High- and Low-excitability rats [40,43]. Using mazes such as the Lat maze, hexagonal tunnel maze, and asymmetric radial arm maze, Sprague–Dawley rats that were vulnerable to display high or low exploratory behavior to spatial novelty tasks were selectively bred together. As compared to randomly bred control rats, the Naples High- and Low-excitability rat strains are hyperreactive and hyporeactive to spatial novelty, respectively (reviewed in Ref. [131]). The different reactivity to novelty in these two rat strains cannot be explained by differences in general motor activity because they do not display significant differences in baseline motor activity [12].

To model differences in the reactivity to novel environments is important to address questions related to the psychiatric disorder known as attention deficit hyperactivity disorder (ADHD), which is characterized by attention impairment with or without impulsiveness, hyperkinesis, restlessness, and timing disturbances [94]. These genetic strains display bidirectional alterations in nonselective (orienting) attention as measured by the duration of rearing episodes, which is reduced to 82% of the random-bred level (assumed as 100%) in the Naples High-excitability strain and increased to 147% in the Naples Low-excitability strain [6]. The Naples strains do not differ in nonspatial learning abilities per se (e.g., associative tasks such as conditioned taste aversion to sweet solutions), but rather in motor reactivity to spatial novelty (i.e., frequency of crossings and rearings in mazes), nonselective attention or orienting in mazes (i.e., duration of each rearing episode), and inattention to reinforcement under low motivational level (i.e., consumption of chocolate in baited arm of maze when not food-deprived) [13]. Both strains have also been found to have lower performance in the Morris water maze task relative to randomly bred controls and higher indices of emotionality as measured by the number of fecal boli deposited in novel environments [131].

There are several variants of ADHD, and the Naples High-excitability rats are presumed to model the ADHD-plus variant (predominantly hyperactive–impulsive type with attention deficit) where rapid attention shifts and hyperactivity prevail, whereas the Naples Low-excitability rats model the ADHD-minus variant (predominantly inattentive type without hyperactivity) with sluggish attention and hyporeactivity [40]. These two genetic strains can be compared to randomly bred rats that show normal attention and motor reactivity to spatial novelty tasks to determine differences in their brain metabolic capacity, which are likely the result of interactions between genetic and environmental factors operating throughout life.

Baseline differences in cytochrome oxidase activity between Naples High- and Low-excitability strains and randomly bred control rats are found in specific regions of the hippocampal formation, cerebral cortex, and subcortical nuclei (Table 3) [40,43]. The only region that showed a significant difference in metabolic capacity between Naples High- and Low-excitability rats was within the hippocampal formation, suggesting that the differences in activity in the hippocampal formation might modulate differences in activity profiles in novel environments [13,43]. Cytochrome oxidase activity in the outer granular cell layer of the dentate gyrus is reduced in Naples Low-excitability rats relative to Naples High-excitability rats. It is relevant that hippocampal activity has been observed during exploratory behavior and rearings [137], and that behavioral arousal to novelty depends on the integrity of the hippocampal formation [14,46,129]. Therefore, the lower neurometabolic capacity of Naples Low-excitability rats could bias them to explore less during spatial novelty tasks. This finding may be of particular relevance to the developmental etiology of the ADHD-minus variant because the granular cells of the dentate gyrus are actively dividing in infants and are thus more vulnerable to postnatal influences that may affect their metabolic capacity. In rats, the granule cells of the dentate gyrus exhibit postnatal cell division and are especially vulnerable during infancy to X-rays that disrupt cell division [29]. Indeed, even before the label ADHD was coined, Altman [3] proposed that dentate granule cell hypoplasia is a key reason for brain dysfunction underlying learning disabilities in children and showed that it could be modeled by X-ray irradiation of infant rats. Therefore, the difference in baseline cytochrome oxidase activity between Naples High- and Low-excitability rats is consistent with previous studies indicating that the dentate granule cells in the hippocampal formation may be critical for the behavioral differences between these two strains [12,13].

Relative to randomly bred controls, Naples Low-excitability rats have increased cytochrome oxidase activity in the medial prefrontal cortex, which might also contribute to their behavioral hyporeactivity but normal baseline motor activity [12]. Increased metabolic activity of the medial prefrontal cortex in normal rodents is correlated with the inhibition of behavior during extinction of instrumental goal-seeking behavior [87] and extinction of Pavlovian

Table 3
Differences between Naples High-excitability, Low-excitability, and randomly bred control Sprague–Dawley male rats in cytochrome oxidase activity

Brain region	Direction of difference in metabolic capacity
Dentate gyrus	Naples Low < Naples High
Medial prefrontal cortex	Naples Low > randomly bred control
Cortical amygdala	Naples High < randomly bred control
Posterior parietal cortex	Naples High < randomly bred control
Perirhinal cortex, ventral	Naples High < randomly bred control
Perirhinal cortex, dorsal	Naples High and Low < randomly bred control

conditioned responses [8]. Subjects with higher medial prefrontal cortex activity are more successful at inhibiting their behavior. Indeed, there is a 0.99 correlation between metabolic activity in the medial prefrontal cortex and extinction of conditioned emotional behavior [8]. Therefore, if we consider hyporeactivity a form of behavioral inhibition, then it is not surprising that increased baseline metabolism in the medial prefrontal cortex is correlated with hyporeactivity in Naples strains.

The Naples rat strains are also different from randomly bred control rats in the metabolic capacity of areas that mediate limbic and spatial attention information [40]. For example, only limbic and cortical regions showed altered cytochrome oxidase activity among over 70 regions analyzed. No sensory or motor nuclei or other subcortical structures were affected in the Naples rats. The only limbic nucleus altered was the cortical amygdala, with lower activity in Naples High-excitability rats relative to randomly bred controls. This is a limbic region whose dysfunction has been linked traditionally to an increase in emotionality that is consistent with the hyperreactivity shown by Naples High-excitability rats [75]. On the other hand, increased metabolic activity in the cortical amygdala has been related to the acquisition of a conditioned defensive response in normal rats [44]. Hence, decreased metabolic capacity in the cortical amygdala could handicap emotional learning and increase the emotionality of Naples High-excitability rats.

Reduced metabolic activity of cortical regions in Naples High-excitability rats may contribute to their particular spatial attention deficit. For example, relative to randomly bred controls, Naples High-excitability rats have reduced metabolic capacity in the posterior parietal cortex and the perirhinal cortex. The posterior parietal cortex is linked to spatial attentional processes in rats [66] and other species, including humans [4]. Humans with posterior parietal cortex lesions have difficulty attending to visual stimuli. Rats with ischemia leading to decreased cytochrome oxidase activity in this region show impaired learning of the Morris water maze—a task that relays on attention to spatial cues [10]. Similarly, aged rats with impaired performance in the water maze have decreased cytochrome oxidase activity in perirhinal cortex compared to unimpaired rats [132], and lesions of the perirhinal cortex lead to deficits in the water maze task [71]. Since posterior parietal and perirhinal metabolism is correlated with spatial learning, it is plausible that reduced baseline metabolic capacity in this region might impair the spatial attention ability of Naples High-excitability rats. It should be mentioned that Naples Low-excitability rats also have lower cytochrome oxidase activity in the dorsal perirhinal cortex relative to randomly bred controls, which might also contribute to their reduced performance in the Morris water maze.

As mentioned in the Introduction, there is a link between cytochrome oxidase activity and glutamatergic stimulation. Strain differences in the glutamatergic system have been studied in Naples rats [106], and it is evident that the relationship between cytochrome oxidase activity and glutamate receptor expression or glutamatergic innervation is not simple. For example, relative to Naples Low-excitability rats, High-excitability rats have more total glutamate binding sites (NMDA and quisqualate receptor binding combined) in the dentate gyrus, which corresponds to their elevated cytochrome oxidase activity in the dentate gyrus. On the other hand, the cytochrome oxidase difference in the medial frontal cortex (Low-excitability strain greater than randomly bred controls) is not associated with a difference in glutamate binding, and differences in glutamate binding in the caudate–putamen are not associated with differences in cytochrome oxidase activity. With regard to glutamatergic input, both Naples High- and Low-excitability strains have a lower density of Zn^{2+}-rich terminals in the hippocampus relative to control rats. However, no significant differences in cytochrome oxidase activity have been found in the hippocampus proper, although there is an overall trend for both Naples High- and Low-excitability rats to have lower hippocampal cytochrome oxidase activity relative to control rats.

Neuroimaging studies in humans have implicated other brain areas in ADHD that fail to show cytochrome oxidase activity differences across the Naples strains or have not been analyzed (reviewed in Ref. [33]). For example, there is evidence that blood flow into the striatum is reduced in individuals with ADHD and that treatment with psychostimulants such as methylphenidate (Ritalin) both alleviates the symptoms of ADHD and increases metabolism in the striatum (e.g., Ref. [63,74,128]). On the other hand, no differences in cytochrome oxidase activity among Naples High- and Low-excitability rats and randomly bred controls have been found in the caudate–putamen or nucleus accumbens. There is also increased focus on the role of the cerebellum in ADHD. Methylphenidate increases regional blood flow in the cerebellum, specifically the cerebellar vermis [5,115,133], and reductions in the total volume of the cerebellum as well as the cerebellar vermis have been noted in ADHD individuals (reviewed in Refs. [33,115]). However, some studies fail to find consistent changes in regional blood flow following psychostimulant treatment [36,77], and other studies report that individual differences in neural responses to methylphenidate correlate with individual differences in the magnitude of ADHD symptoms (e.g. Ref. [5]) or abundance of dopamine receptors [133]. We currently do not know whether these Naples strains show different levels of cytochrome oxidase activity within the cerebellum, although this would be of great interest.

5. Summary and conclusion

We reviewed here our cytochrome oxidase studies analyzing baseline neurometabolic differences caused by embryonic and genetic backgrounds in naïve animals, and correlated these neural differences with differences in

behavioral predispositions. Our motivation for studying these brain–behavior parallels lies in the notion that baseline metabolic differences in regional neural activity in pertinent neural circuits could predict behavioral phenotype. The baseline level of metabolic activity or capacity in specific neural circuits, which is intimately related to cytochrome oxidase activity, could affect the propensity to the display of specific behaviors.

When examining the neurometabolic correlates of differences in social behaviors caused by developmental factors, we noted that increased neurometabolic capacity in the anterior hypothalamus was correlated with increased capacity for androgen administration in adulthood to elicit male-typical social behaviors in female gerbils and leopard geckos. For example, female leopard geckos that hatched from eggs incubated at 32.5 °C have elevated cytochrome oxidase activity in the anterior hypothalamus and are more likely to display aggression and courtship behavior following androgen treatment in adulthood [20,22]. In male and female leopard geckos but not female gerbils, increased cytochrome oxidase activity in the preoptic area, an evolutionarily conserved nucleus governing the display of male-typical sexual behavior, is also correlated with a heightened proclivity to display courtship behavior following androgen treatment. Furthermore, incubation temperature-induced increases in aggressiveness toward intruders are paralleled by increases in metabolic capacity in amygdaloid areas in male and female leopard geckos (although some areas show different relationships between males and females; see above). All of these nuclei express receptors for sex steroid hormones, are active during the display of social behaviors, and have been implicated in the control of social behaviors (reviewed in Refs. [21,81,96,97]).

When examining the neurometabolic correlates of genetic differences in the propensity to display learned helplessness (selective breeding paradigm), rats that are predisposed to display learned helplessness have elevated cytochrome oxidase activity in areas such as paraventricular hypothalamus, infralimbic cortex, hippocampal formation, and habenula, and lower cytochrome oxidase activity in areas such as the dorsal prefrontal cortex, ventral tegmental area, basolateral and central amygdaloid nuclei, and basal ganglia relative to rats that are resistant to display learned helplessness. These baseline metabolic differences are similar to those found between depressed and nondepressed humans and relate to differences in the hypothalamic–pituitary–adrenal axis (stress response), anhedonia, and psychomotor retardation (reviewed in Ref. [118]).

The Naples High- and Low-excitability rats are strains of rats selectively bred to display high and low levels of activity, respectively, when tested in spatial novelty tasks in various mazes, and have been argued to be useful models for features of ADHD. The Naples High- and Low-excitability lines show deficits in spatial learning tasks such as the Morris water maze but do not show deficits in nonspatial learning tasks such as shock motivated two-way active avoidance in shuttle box or conditioned taste aversion [13]. Low-excitability rats have reduced cytochrome oxidase activity in the dentate gyrus, and because behavioral responses to spatial novelty are affected by the hippocampal formation, the lower metabolic activity in Low-excitability rats could account for their lower activity scores when tested in novel environments. On the other hand, Low-excitability rats have higher cytochrome oxidase activity in the medial prefrontal cortex, which may contribute to the behavioral inhibition they manifest in novel environments. The spatial deficits observed in the Naples High-excitability rats are paralleled by decreased cytochrome oxidase activity in the posterior parietal and perirhinal cortices—areas involved in spatial processing and memory. Although Naples High-excitability rats have lower cytochrome oxidase activity in the cortical amygdala relative to randomly bred controls, no difference in cytochrome oxidase activity was found in the basolateral and central amygdaloid nuclei. Because the basolateral and central amygdala have been implicated in associative learning tasks such as shock avoidance and taste aversion, the lack of differences in cytochrome oxidase activity in these two nuclei is correlated with a lack of differences in shock avoidance learning and conditioned taste aversion among Naples strains.

Although comparisons and contrasts of brain–behavior correlations across model systems would be ideal, this is difficult because each model system was selected for disparate purposes. Because the behavioral differences varied across model systems, different brain nuclei were highlighted. There are, however, some common behavioral phenotypes across systems, and it is important to assess the similarity in the neurometabolic substrates of these differences. For example, just as leopard geckos from cooler incubation temperatures are less aggressive than geckos from warmer incubation temperatures, congenitally helpless rats are less dominant relative to congenitally nonhelpless male rats. In the leopard gecko, less aggressive individuals have lower metabolic capacity in areas like the septum and amygdala, and, similarly, congenitally helpless rats have lower cytochrome oxidase activity in the septum and some amygdaloid nuclei.

There is evidence that learned helpless animals show attention deficits and that this may contribute to their learning impairments, at least under certain environmental conditions [69,82]. For example, just as Naples High- and Low-excitability rats show poorer performance in the Morris water maze relative to randomly bred controls [131], congenitally helpless male rats show learning deficits in the Morris water maze relative to congenitally nonhelpless rats [65]. However, there are few similarities in the regions in which congenitally helpless rats and the Naples rat strains differ in metabolic capacity from their respective control groups (Tables 2 and 3). The degree of similarity in behavioral phenotype is not known between congenitally learned helpless rats and Naples rats, and given the lack of

neurometabolic similarities, it is plausible that the attention deficits exhibited by congenitally helpless rats are different from those exhibited by Naples rats.

It will be interesting to assess how differences in baseline cytochrome oxidase expression affect neuronal responsiveness to experimental manipulations. For example, because cytochrome oxidase is a rate-limiting enzyme in ATP synthesis, it is possible that differences in cytochrome oxidase activity parallel difference in the degree to which specific manipulations activate pertinent brain regions. For example, rats that became helpless following inescapable shock showed lower expression of immediate early genes in the septum following a stressor [124], and it is possible that stressors would differentially activate septal neurons in congenitally helpless and nonhelpless rats. Differential neuronal responses to spatial novelty have been reported across the Naples strains. Naples High-excitability rats, which have greater cytochrome oxidase expression the dentate gyrus than Naples Low-excitability rats, show greater FOS expression in the hippocampus following exposure to a novel environment than Naples-Low excitability rats [93].

Differences in cytochrome oxidase activity between groups are likely to be caused by differences in metabolic history and can have several potential consequences. Increased neural activity can cause increases in the expression and activity of cytochrome oxidase in particular brain areas. Increased cytochrome oxidase activity is linked to larger and more numerous neuronal mitochondria, and mitochondria modulate intracellular Ca^{+2} concentrations, which can affect Ca^{+2}-dependent plasticity mechanisms. Mitochondria can also regulate synaptic plasticity in areas like the hippocampus and neuromuscular junction (e.g., Refs. [70,125]). Higher cytochrome oxidase activity is likely to correlate with elevated baseline firing rates [139], and higher baseline firing rates have been found to correlate with heightened neural and behavioral plasticity (e.g., Refs. [80,116]). This suggests that differences in cytochrome oxidase activity could lead to differences in behavioral and neural plasticity.

In the leopard gecko, variation in baseline cytochrome oxidase activity is linked to variation in behavioral and neurometabolic responses to experimental manipulations (reviewed in Ref. [110]). For example, male leopard geckos from the female-biased incubation temperature have elevated cytochrome oxidase activity in the preoptic area, which has been implicated in experience-dependent changes in social behavior, and these males show greater changes in territorial and conditioning-like behaviors following social interactions with females [109]. Regarding neurometabolic plasticity, female leopard geckos from the low and male-biased incubation temperatures differ in cytochrome oxidase activity in a variety of nuclei and show different changes in metabolic capacity following hormone manipulations and sociosexual experience (cohabitation with a male). For instance, females from the male-biased incubation temperature have elevated cytochrome oxidase activity in areas like the anterior hypothalamus, external nucleus of the amygdala, and preoptic area relative to females from the low incubation temperature, and, following ovariectomy, metabolic capacity in these three areas decreases only in females from the male-biased incubation temperature [22]. In response to sociosexual experience, metabolic capacity increases in the external nucleus of the amygdala and preoptic area in both females. However, experience-dependent increases in the lateral hypothalamus are found only in females from the low incubation temperature, and experience-dependent increases in the ventromedial hypothalamus are found only in females from the male-biased incubation temperature [23]. This suggests that baseline neurometabolism could influence neurometabolic plasticity, and it will be important to assess variation in neurometabolic plasticity in the other model systems.

Our goal for this review has been to emphasize that, whereas cytochrome oxidase activity is usually viewed as an endpoint in experiments involving behavioral or neural manipulations, endogenous differences in baseline neural metabolic capacity (cytochrome oxidase activity) can also serve as a starting point to predict behavioral differences. Specific behavioral variations caused by genetic and developmental factors correlate with differences in cytochrome oxidase activity in specific brain areas, and we hypothesize that differences in baseline neural metabolic capacity are one of the mechanisms by which behavioral variation is generated.

Acknowledgements

This work received funding from NSF DGE-9616181 (J.T.S.), NIH NS07067-25 (J.T.S.), NIMH 41770 (D.C.), NIMH 57874 (D.C.), and NIH NS37755 (F.G.L). We thank two anonymous reviewers for their helpful comments.

References

[1] H.C. Abercrombie, S.M. Schaefer, C.L. Larson, T.R. Oakes, K.A. Lindgren, J.E. Holden, S.B. Perlman, P.A. Turski, D.D. Krahn, R.M. Benca, R.J. Davidson, Metabolic rate in the right amygdala predicts negative affect in depressed patients, NeuroReport 9 (1998) 3301–3307.

[2] D.J. Albert, R.H. Jonik, M.L. Walsh, Hormone-dependent aggression in male and female rats: experiential, hormonal, and neural foundations, Neurosci. Biobehav. Rev. 16 (1992) 177–192.

[3] J. Altman, An animal model of minimal brain dysfunction, in: M. Lewis (Ed.), Learning Disabilities and Prenatal Risk, University of Illinois, Chicago, 1986, pp. 241–304.

[4] R.A. Andersen, Inferior parietal lobule function in spatial perception and visuomotor integration, in: F. Plum (Ed.), Handbook of Physiology: Section 1. The Nervous System: Vol. VI. Higher Functions of the Brain: Part 2, American Physiological Society, Maryland, 1987, pp. 483–518.

[5] C.M. Anderson, A. Polcari, S.B. Lowen, P.F. Renshaw, M.H. Teicher, Effects of methylphenidate on functional magnetic reso-

nance relaxometry of the cerebellar vermis in boys with ADHD, Am. J. Psychiatry 159 (2002) 1322–1328.
[6] R. Aspide, U.A.G. Carnevale, J.A. Sergeant, A.G. Sadile, Non-selective attention and nitric oxidase in putative animal models of attention-deficit hyperactivity disorder, Behav. Brain Res. 95 (1998) 123–133.
[7] M. Baily, M. Rydz, L. Kaczmarek, Precontact 50-kHz vocalization in male rats during acquisition of sexual experience, Behav. Neurosci. 114 (2000) 983–990.
[8] D. Barrett, J. Shumake, D. Jones, F. Gonzalez-Lima, Metabolic mapping of mouse brain activity after extinction of a conditioned emotional response, J. Neurosci. 23 (2003) 5740–5749.
[9] I.W. Borowsky, R.C. Collins, Histochemical changes in enzymes of energy metabolism in the dentate gyrus accompany deafferentation and synaptic reorganization, Neuroscience 33 (1989) 253–262.
[10] A. Cada, J.C. de la Torre, F. Gonzalez-Lima, Chronic cerebrovascular ischemia in aged rats: effects on brain metabolic capacity and behavior, Neurobiol. Aging 21 (2000) 225–233.
[11] S. Caldecott-Hazard, J. Mazziotta, M. Phelps, Cerebral correlates of depressed behavior in rats, visualized using ^{14}C-2-deoxyglucose autoradiography, J. Neurosci. 8 (1988) 1951–1961.
[12] A. Cerbone, F.R. Patacchioli, A.G. Sadile, A neurogenetic and morphogenetic approach to hippocampal functions based on individual differences and neurobehavioral covariations, Behav. Brain Res. 55 (1993) 1–16.
[13] A. Cerbone, M.P. Pellicano, A.G. Sadile, Evidence of and against the Naples high- and low-excitability rats as genetic model to study hippocampal functions, Neurosci. Biobehav. Rev. 17 (1993) 295–303.
[14] B.S. Chozick, The behavioral effects of lesions of the hippocampus: a review, Int. J. Neurosci. 15 (1983) 295–304.
[15] M.M. Clark, B.G. Galef Jr., Effects of uterine position on rate of sexual development in female Mongolian gerbils, Physiol. Behav. 42 (1988) 15–18.
[16] M.M. Clark, B.G. Galef Jr., Prenatal influences on reproductive life history strategies, Trends Ecol. Evol. 10 (1995) 151–153.
[17] M.M. Clark, C.A. Spencer, B.G. Galef Jr., Improving the productivity of breeding colonies of Mongolian gerbils (*Meriones unguiculatus*), Lab. Anim. 20 (1986) 313–315.
[18] M.M. Clark, D. Crews, B.G. Galef Jr., Concentrations of sex steroid hormones in pregnant and fetal Mongolian gerbils, Physiol. Behav. 49 (1991) 239–243.
[19] B. Cooke, C.D. Hegstrom, L.S. Villeneuve, S.M. Breedlove, Sexual differentiation of the vertebrate brain: principles and mechanisms, Front. Neuroendocrinol. 19 (1998) 323–362.
[20] P. Coomber, D. Crews, F. Gonzalez-Lima, Independent effects of incubation temperature and gonadal sex on the volume and metabolic capacity of brain nuclei in the leopard gecko (*Eublepharis macularius*), a lizard with temperature-dependent sex determination, J. Comp. Neurol. 380 (1997) 409–421.
[21] D. Crews, R. Silver, Reproductive physiology and behavior interactions in nonmammalian vertebrates, in: N. Adler, D. Pfaff, R.W. Goy (Eds.), Handbook of Behavioral Neurobiology, vol. 7, Plenum Press, New York, 1985, pp. 101–185.
[22] D. Crews, P. Coomber, R. Baldwin, N. Azad, F. Gonzalez-Lima, Brain organization in a reptile lacking sex chromosomes: effects of gonadectomy and exogenous testosterone, Horm. Behav. 30 (1996) 474–486.
[23] D. Crews, P. Coomber, F. Gonzalez-Lima, Effects of age and sociosexual experience on the morphology and metabolic capacity of brain nuclei in the leopard gecko (*Eublepharis macularius*), a lizard with temperature-dependent sex determination, Brain Res. 758 (1997) 169–179.
[24] D. Crews, J. Sakata, T. Rhen, Developmental effects on intersexual and intrasexual variation in growth and reproduction in a lizard with temperature-dependent sex determination, Comp. Biochem. Physiol., C 119 (1998) 229–241.
[25] A.M. Davis, S.C. Ward, M. Selmanoff, A.E. Herbison, M.M. McCarthy, Developmental sex differences in amino acid neurotransmitter levels in hypothalamic and limbic areas of rat brain, Neuroscience 90 (1999) 1471–1482.
[26] Y. Delville, G.J. de Vries, C.F. Ferris, Neural connections of the anterior hypothalamus and agonistic behavior in golden hamsters, Brain Behav. Evol. 55 (2000) 53–76.
[27] M.D. Devous Sr., M.H. Trivedi, A.J. Rush, Regional cerebral blood flow response to oral amphetamine challenge in healthy volunteers, J. Nucl. Med. 42 (2001) 535–542.
[28] E.A. Deyoe, T.C. Trusk, M.T. Wong-Riley, Activity correlates of cytochrome oxidase-defined compartments in granular and supragranular layers of primary visual cortex of the macaque monkey, Vis. Neurosci. 12 (1995) 629–639.
[29] J.L. Diaz-Granados, P.L. Greene, A. Amsel, Selective activity enhancement and persistence in weenling rats after hippocampal irradiation in infancy: possible relevance for ADHD, Behav. Neural Biol. 61 (1994) 251–259.
[30] W.C. Drevets, Neuroimaging and neuropathological studies of depression: implications for the cognitive–emotional features of mood disorders, Curr. Opin. Neurobiol. 11 (2001) 240–249.
[31] W.C. Drevets, W. Bogers, M.E. Raichle, Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism, Eur. Neuropsychopharmacol. 12 (2002) 527–544.
[32] W.C. Drevets, J.L. Price, M.E. Bardgett, T. Reich, R.D. Todd, M.E. Raichle, Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels, Pharmacol. Biochem. Behav. 71 (2002) 431–447.
[33] S. Durston, A review of the biological bases of ADHD: what have we learned from imaging studies, Ment. Retard. Dev. Disabil. Res. Rev. 9 (2003) 184–195.
[34] E. Edwards, J. Johnson, D. Anderson, P. Turano, F.A. Henn, Neurochemical and behavioral consequences of mild, uncontrollable shock: effects of PCPA, Pharmacol. Biochem. Behav. 25 (1986) 415–421.
[35] M. Erecinska, I.A. Silver, ATP and brain function, J. Cereb. Blood Flow Metab. 9 (1989) 2–19.
[36] M. Ernst, A.J. Zametkin, J.A. Matochik, L. Liebenauer, G.A. Fitzgerald, R.M. Cohen, Effects of intravenous dextroamphetamine on brain metabolism in adults with attention-deficit hyperactivity disorder—preliminary findings, Psychopharmacol. Bull. 30 (1994) 219–225.
[37] M.S. Fanselow, J.E. LeDoux, Why we think plasticity underlying Pavlovian fear conditioning occurs in the basolateral amygdala, Neuron 23 (1999) 229–232.
[38] D.L. Flores, D. Crews, Effect of hormonal manipulation on sociosexual behavior in adult female leopard geckos (*Eublepharis macularius*), a species with temperature-dependent sex determination, Horm. Behav. 29 (1995) 458–473.
[39] D. Flores, A. Tousignant, D. Crews, Incubation temperature affects the behavior of adult leopard geckos (*Eublepharis macularius*), Physiol. Behav. 55 (1994) 1067–1072.
[40] A. Gallo, F. Gonzalez-Lima, A.G. Sadile, Impaired metabolic capacity in the perirhinal and posterior parietal cortex lead to dissociation between attentional, motivational and spatial components of exploration in the Naples High-Excitability rat, Behav. Brain Res. 130 (2002) 133–140.
[41] F. Gonzalez-Lima, Brain imaging of auditory learning functions in rats: studies with fluorodeoxyglucose autoradiography and cytochrome oxidase histochemistry, in: F. Gonzalez-Lima (Ed.), Advances in Metabolic Mapping Techniques for Brain Imaging of Behavioral and Learning Functions, Kluwer Academic Publishers, Dordrecht, 1992, pp. 39–109.
[42] F. Gonzalez-Lima, A. Cada, Cytochrome oxidase atlas of rat brain, in: F. Gonzalez Lima (Ed.), Cytochrome Oxidase in Neuronal Metabolism and Alzheimer's Disease, Plenum, New York, 1998, pp. 263–280.

[43] F. Gonzalez-Lima, A.G. Sadile, Network operations revealed by brain metabolic mapping and genetic model of hyperactivity and attention deficit: the Naples high- and low-excitability rats, Neurosci. Biobehav. Rev. 24 (2000) 157–160.
[44] F. Gonzalez-Lima, H. Scheich, Classical conditioning of tone-signaled bradycardia modifies 2-deoxyglucose uptake patterns in cortex, thalamus, habenula, caudate–putamen and hippocampal formation, Brain Res. 363 (1986) 239–256.
[45] J.L. Goodson, R. Eibach, J. Sakata, E. Adkins-Regan, Effect of septal lesions on male song and aggression in the colonial zebra finch (*Taeniopygia guttata*) and the territorial field sparrow (*Spizella pusilla*), Behav. Brain Res. 10 (1999) 115–128.
[46] J.A. Gray, N. McNaughton, Comparison between the behavioral effects of septal and hippocampal lesions: a review, Neurosci. Biobehav. Rev. 7 (1983) 119–188.
[47] N. Greenberg, M. Scott, D. Crews, Role of the amygdala in the reproductive and aggressive behavior of the lizard, *Anolis carolinensis*, Physiol. Behav. 32 (1984) 147–151.
[48] M. Halpern, The organization and function of the vomeronasal system, Annu. Rev. Neurosci. 10 (1987) 325–362.
[49] S. Hamann, R.A. Herman, C.L. Nolan, K. Wallen, Men and women differ in amygdala response to visual sexual stimuli, Nat. Neurosci. 4 (2004) 411–416.
[50] R.P. Hammer Jr., W.S. Pires, A. Markou, G.F. Koob, Withdrawal following cocaine self-administration decreases regional cerebral metabolic rate in critical brain reward regions, Synapse 14 (1993) 73–80.
[51] F.A. Henn, E. Edwards, Animal models in the study of genetic factors in human psychopathology, in: D.F. Papolos, H.M. Lachman (Eds.), Genetic Studies in Affective Disorders: Overview of Basic Methods, Current Directions, and Critical Research Issues, Wiley, New York, pp. 177-192.
[52] R.F. Hevner, M.T. Wong-Riley, Brain cytochrome oxidase: purification, antibody production, and immunohistochemical/histochemical correlations in the CNS, J. Neurosci. 9 (1989) 3884–3898.
[53] R.F. Hevner, M.T. Wong-Riley, Regulation of cytochrome oxidase protein levels by functional activity in the macaque monkey visual system, J. Neurosci. 10 (1990) 1331–1340.
[54] R.F. Hevner, M.T. Wong-Riley, Neuronal expression of nuclear and mitochondrial genes for cytochrome oxidase (CO) subunits analyzed by in situ hybridization: comparison with CO activity and protein, J. Neurosci. 11 (1991) 1942–1958.
[55] R.F. Hevner, M.T. Wong-Riley, Mitochondrial and nuclear gene expression for cytochrome oxidase subunits are disproportionately regulated by functional activity in neurons, J. Neurosci. 13 (1993) 1805–1819.
[56] R.F. Hevner, R.S. Duff, M.T. Wong-Riley, Coordination of ATP production and consumption in brain: parallel regulation of cytochrome oxidase and Na^+, $K(^+)$-ATPase, Neurosci. Lett. 138 (1992) 188–192.
[57] R.F. Hevner, S. Liu, M.T. Wong-Riley, A metabolic map of cytochrome oxidase in the rat brain: histochemical, densitometric and biochemical studies, Neuroscience 65 (1995) 313–342.
[58] E.M. Hull, J. Du, D.S. Lorrain, L. Matuszewich, Testosterone, preoptic dopamine, and copulation in male rats, Brain Res. Bull. 44 (1997) 327–333.
[59] D. Jones, F. Gonzalez-Lima, D. Crews, B.G. Galef Jr., M.M. Clark, Effects of intrauterine position on the metabolic capacity of the hypothalamus of female gerbils, Physiol. Behav. 61 (1997) 513–519.
[60] G.H. Kageyama, M.T. Wong-Riley, Histochemical localization of cytochrome oxidase in the hippocampus: correlation with specific neuronal types and afferent pathways, Neuroscience 7 (1982) 2337–2361.
[61] G.H. Kageyama, M. Wong-Riley, Laminar and cellular localization of cytochrome oxidase in the cat striate cortex, J. Comp. Neurol. 245 (1986) 137–159.
[62] G.H. Kageyama, M. Wong-Riley, Differential effect of visual deprivation on cytochrome oxidase levels in major cells classes of the cat LGN, J. Comp. Neurol. 246 (1986) 212–237.
[63] B.-N. Kim, J.-S. Lee, S.-C. Cho, D.-S. Lee, Methylphenidate increased regional cerebral blood flow in subjects with attention deficit/hyperactivity disorder, Yonsei Med. J. 42 (2001) 19–29.
[64] T.A. Kimbrell, T.A. Ketter, M.S. George, J.T. Little, B.E. Benson, M.W. Willis, P. Herscovitch, R.M. Post, Regional cerebral glucose utilization in patients with a range of severities of unipolar depression, Biol. Psychiatry 51 (2002) 237–252.
[65] J.A. King, S. Abend, E. Edwards, Genetic predisposition and the development of posttraumatic stress disorder in an animal model, Biol. Psychiatry 50 (2001) 231–237.
[66] B. Kolb, J. Walkey, Behavioral and anatomical studies of the posterior parietal cortex in the rat, Behav. Brain Res. 23 (1987) 127–145.
[67] S.W. Kollack-Walker, S.W. Newman, Mating and agonistic behavior produce different patterns of Fos immunolabeling in the male Syrian hamster brain, Neuroscience 66 (1995) 721–736.
[68] H.M. Lachman, D.F. Papolos, A. Boyle, G. Sheftel, M. Juthani, E. Edwards, F.A. Henn, Alterations in glucocorticoid inducible RNAs in the limbic system of learned helpless rats, Brain Res. 609 (1993) 110–116.
[69] R.K. Lee, S.F. Maier, Inescapable shock and attention to internal versus external cues in a water discrimination escape task, J. Exp. Psychol., Anim. Behav. Processes 14 (1988) 302–310.
[70] M. Levy, G.C. Faas, P. Saggau, W.J. Craigen, J.D. Sweatt, Mitochondrial regulation of synaptic plasticity in the hippocampus, J. Biol. Chem. 278 (2003) 17727–17734.
[71] P. Liu, D.K. Bilkey, Perirhinal cortex contributions to performance in the Morris water maze, Behav. Neurosci. 112 (1998) 304–315.
[72] Q. Liu, M.T. Wong-Riley, Postnatal expression of neurotransmitters, receptors, and cytochrome oxidase in the rat pre-Botzinger complex, J. Appl. Physiol. 92 (2002) 923–934.
[73] S. Liu, M. Wong-Riley, Disproportionate regulation of nuclear- and mitochondrial-encoded cytochrome oxidase subunit proteins by functional activity in neurons, Neuroscience 67 (1995) 197–210.
[74] H.C. Lou, L. Henriksen, P. Bruhn, Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder, Arch. Neurol. 41 (1984) 825–829.
[75] I. Lukaszewska, R. Korczynski, A. Markowska, E. Kostarczyk, Emotionality and exploratory behavior following cortico-basomedial amygdala lesion in rat, Acta Neurobiol. Exp. 40 (1980) 911–932.
[76] F. Maier, R.E. Grahn, B.A. Kalman, L.C. Sutton, E.P. Wiertelak, L.R. Watkins, The role of the amygdala and dorsal raphe nucleus in mediating the behavioral consequences of inescapable shock, Behav. Neurosci. 107 (1993) 377–388.
[77] J.A. Matochik, L.L. Liebenauer, A.C. King, H.V. Szymanski, R.M. Cohen, A.J. Zametkin, Cerebral glucose metabolism in adults with attention deficit hyperactivity disorder after chronic stimulant treatment, Am. J. Psychiatry 151 (1994) 658–664.
[78] H.S. Mayberg, S.K. Brannan, J.L. Tekell, J.A. Silva, R.K. Mahurin, S. McGinnis, P.A. Jerabek, Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response, Biol. Psychiatry 48 (2000) 830–843.
[79] M.M. McCarthy, A.M. Davis, J.A. Mong, Excitatory neurotransmission and sexual differentiation of the brain, Brain Res. Bull. 44 (1997) 487–495.
[80] M.D. McEchron, A.P. Weible, J.F. Disterhoft, Aging and learning-specific changes in single-neuron activity in CA1 hippocampus during rabbit trace eyeblink conditioning, J. Neurophysiol. 86 (2001) 1839–1857.
[81] R.L. Meisel, B.D. Sachs, The physiology of male sexual behavior, in: E. Knobil, J.D. Neill (Eds.), The Physiology of Reproduction, vol. 1, Raven Press, New York, 1994, pp. 3–105.
[82] T.R. Minor, R.L. Jackson, S.F. Maier, Effects of task-irrelevant cues and reinforcement delay on choice-escape learning following

inescapable shock: evidence for a deficit in selective attention, J. Exp. Psychol., Anim. Behav. Processes 10 (1984) 543–556.
[83] A.E. Mjaatvedt, M.T. Wong-Riley, Relationship between synaptogenesis and cytochrome oxidase activity in Purkinje cells of the developing rat cerebellum, J. Comp. Neurol. 277 (1988) 155–182.
[84] A.E. Mjaatvedt, M.T. Wong-Riley, Effects of unilateral climbing fibre deafferentation on cytochrome oxidase activity in the developing rat cerebellum, J. Neurocytol. 20 (1991) 2–16.
[85] C.L. Moore, The role of maternal stimulation in the development of sexual behavior and its neural basis, Ann. N.Y. Acad. Sci. 662 (1992) 167–177.
[86] K. Nader, J.E. LeDoux, Inhibition of the mesoamygdala dopaminergic pathway impairs the retrieval of conditioned fear associations, Behav. Neurosci. 113 (1999) 891–901.
[87] H.P. Nair, J.D. Berndt, D. Barrett, F. Gonzalez-Lima, Maturation of extinction behavior in infant rats: large-scale interactions with medial prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex, J. Neurosci. 15 (2001) 4400–4407.
[88] F. Nie, M.T. Wong-Riley, Double labeling of GABA and cytochrome oxidase in the macaque visual cortex: quantitative EM analysis, J. Comp. Neurol. 356 (1995) 115–131.
[89] F. Nie, M.T. Wong-Riley, Mitochondrial- and nuclear-encoded subunits of cytochrome oxidase in neurons: differences in compartmental distribution, correlation with enzyme activity, and regulation by neuronal activity, J. Comp. Neurol. 373 (1996) 139–155.
[90] F. Nie, M.T. Wong-Riley, Differential glutamatergic innervation in cytochrome oxidase-rich and -poor regions of the macaque striate cortex: quantitative EM analysis of neurons and neutrophil, J. Comp. Neurol. 369 (1996) 571–590.
[91] F. Nie, M. Wong-Riley, Nuclear respiratory factor-2 subunit protein: correlation with cytochrome oxidase and regulation by functional activity in the monkey primary visual cortex, J. Comp. Neurol. 404 (1999) 310–320.
[92] M. Palkovits, Stress-induced expression of co-localized neuropeptides in hypothalamic and amygdaloid neurons, Eur. J. Pharmacol. 405 (2000) 161–166.
[93] M. Papa, M.P. Pellicano, A. Cerbone, C. Lamberti-D'Mello, T. Menna, C. Buono, A. Giuditta, H. Welzl, A.G. Sadile, Immediate early genes and brain DNA remodeling in the Naples High- and Low-excitability rat lines following exposure to spatial novelty, Brain Res. Bull. 37 (1995) 111–118.
[94] M. Papa, A.G. Sadile, J.A. Sergeant, J. Shumake, F. Gonzalez-lima, Functional imaging probes to study the neural bases of behavior in genetic animal models of ADHD: a comparative analysis of short and long-term markers of neuronal activity, in: F. Gonzalez-Lima (Ed.), Cytochrome Oxidase in Neuronal Metabolism and Alzheimer's Disease, Plenum, New York, 1998, pp. 145–170.
[95] F. Petty, A.D. Sherman, GABAergic modulation of learned helplessness, Pharmacol. Biochem. Behav. 15 (1981) 567–570.
[96] D.W. Pfaff, A.P. Arnold, A.M. Etgen, S.E. Fahrbach, R.T. Rubin (Eds.), Hormones, Brain, and Behavior, vols. 1–5, Academic Press, Amsterdam, 2002.
[97] J.G. Pfaus, T.E. Kippin, S. Centeno, Conditioning and sexual behavior, Horm. Behav. 40 (2001) 291–321.
[98] A. Poremba, D. Jones, F. Gonzalez-Lima, Classical conditioning modifies cytochrome oxidase activity in the auditory system, Eur. J. Neurosci. 10 (1998) 3035–3043.
[99] W.S. Powell, J.M. Dominguez, E.M. Hull, An NMDA antagonist impairs copulation and experience-induced enhancement of male sexual behavior in the rat, Behav. Neurosci. 117 (2003) 69–75.
[100] T. Rhen, D. Crews, Embryonic temperature and gonadal sex organize male-typical sexual and aggressive behavior in a lizard with temperature-dependent sex determination, Endocrinology 140 (1999) 4501–4508.
[101] T. Rhen, D. Crews, Distribution of androgen and estrogen receptor mRNA in the brain and reproductive tissues of the leopard gecko, *Eublepharis macularius*, J. Comp. Neurol. 437 (2001) 385–397.
[102] T. Rhen, J.T. Sakata, M. Zeller, D. Crews, Sex steroid levels across the reproductive cycle of female leopard geckos, *Eublepharis macularius*, from different incubation temperatures, Gen. Comp. Endocrinol. 118 (2000) 322–331.
[103] L.V. Riters, P. Absil, J. Balthazart, Effects of brain testosterone implants on appetitive and consummatory components of male sexual behavior in Japanese quail, Brain Res. Bull. 47 (1998) 69–79.
[104] M.A. Rogers, J.L. Bradshaw, C. Pantelis, J.G. Phillips, Frontostriatal deficits in unipolar major depression, Brain Res. Bull. 47 (1998) 297–310.
[105] B.C. Ryan, J.G. Vandenbergh, Intrauterine position effects, Neurosci. Biobehav. Rev. 26 (2002) 665–678.
[106] A.G. Sadile, M.P. Pellicano, T. Sagvolden, J.A. Sergeant, NMDA and non-NMDA sensitive [L-^{3}H]glutamate receptor binding in the brain of the Naples high- and low-excitability rats: an autoradiographic study, Behav. Brain Res. 78 (1996) 163–174.
[107] T.J. Sajdyk, D.A. Schober, D.R. Gehlert, A. Shekhar, Role of corticotropin-releasing factor and urocortin within the basolateral amygdala of rats in anxiety and panic responses, Behav. Brain Res. 100 (1999) 207–215.
[108] T.J. Sajdyk, D.A. Schober, D.R. Gehlert, Neuropeptide Y receptor subtypes in the basolateral nucleus of the amygdala modulate anxiogenic responses in rats, Neuropharmacology 43 (2002) 1165–1172.
[109] J.T. Sakata, D. Crews, Embryonic experience shapes behavioural change following social experience in male leopard geckos, *Eublepharis macularius*, Anim. Behav. 66 (2003) 839–846.
[110] J.T. Sakata, D. Crews, Developmental sculpting of social phenotype and plasticity, Neurosci. Biobehav. Rev. 28 (2004) 95–112.
[111] J.T. Sakata, D. Crews, Cytochrome oxidase activity in the preoptic area correlates with differences in sexual behavior of intact and castrated male leopard geckos, *Eublepharis macularius*, Behav. Neurosci. 118 (2004) 857–862.
[112] J.T. Sakata, A. Gupta, F. Gonzalez-Lima, D. Crews, Heterosexual housing increases robustness to castration and metabolic capacity in limbic nuclei in male whiptail lizards, *Cnemidophorus inornatus*, Horm. Behav. 42 (2002) 263–273.
[113] J.T. Sakata, F. Gonzalez-Lima, A. Gupta, D. Crews, Differential elevations in brain metabolic capacity in response to sociosexual experience in the male rat, Brain Res. 936 (2002) 27–37.
[114] J.T. Sakata, A. Gupta, C.P. Chuang, D. Crews, Social experience affects territorial and reproductive behaviours in male leopard geckos, *Eublepharis macularius*, Anim. Behav. 63 (2002) 487–493.
[115] J.B. Schweitzer, D.O. Lee, R.B. Hanford, M.A. Tagamets, J.M. Hoffman, S.T. Grafton, C.D. Kilts, A positron emission tomography study of methylphenidate in adults with ADHD: alterations in resting blood flow and predicting treatment response, Neuropsychopharmacology 28 (2003) 967–973.
[116] B. Setlow, G. Schoenbaum, M. Gallagher, Neural encoding in ventral striatum during olfactory discrimination learning, Neuron 38 (2003) 625–638.
[117] J.D. Shepard, K.W. Barron, D.A. Myers, Corticosterone delivery to the amygdala increases corticotropin-releasing factor mRNA in the central amygdaloid nucleus and anxiety-like behavior, Brain Res. 86 (2000) 288–295.
[118] J. Shumake, F. Gonzalez-Lima, Brain systems underlying susceptibility to helplessness and depression, Behav. Cogn. Neurosci. Rev. 3 (2003) 198–221.
[119] J. Shumake, A. Poremba, E. Edwards, F. Gonzalez-Lima, Congenital helpless rats as a genetic model for cortex metabolism in depression, NeuroReport 11 (2000) 3793–3798.
[120] J. Shumake, E. Edwards, F. Gonzalez-Lima, Hypermetabolism of paraventricular hypothalamus in the congenitally helpless rat, Neurosci. Lett. 311 (2001) 45–48.
[121] J. Shumake, E. Edwards, F. Gonzalez-Lima, Dissociation of septohippocampal metabolism in the congenitally helpless rat, Neuroscience 114 (2002) 373–377.

[122] J. Shumake, E. Edwards, F. Gonzalez-Lima, Opposite metabolic changes in the habenula and ventral tegmental areas of a genetic model of helpless behavior, Brain Res. 963 (2003) 274–281.
[123] D.A. Simmons, P. Yahr, GABA and glutamate in mating-activated cells in the preoptic area and medial amygdala of male gerbils, J. Comp. Neurol. 459 (2003) 290–300.
[124] M. Steciuk, M. Kram, G.L. Kramer, F. Petty, Decrease in stress-induced c-Fos-like immunoreactivity in the lateral septal nucleus of learned helpless rats, Brain Res. 822 (1999) 256–259.
[125] Y.-G. Tang, R.S. Zucker, Mitochondrial involvement in post-tetanic potentiation of synaptic transmission, Neuron 18 (1997) 483–491.
[126] R.S. Tarr, Role of the amygdala in the intraspecies aggressive behavior of the Iguanid lizard, *Sceloporus occidentalis*, Physiol. Behav. 18 (1977) 1153–1158.
[127] A. Tousignant, D. Crews, Incubation temperature and gonadal sex affect growth and physiology in the leopard gecko (*Eublepharis macularius*), a lizard with temperature-dependent sex determination, J. Morphol. 224 (1995) 15–170.
[128] C.J. Vaidya, G. Austin, G. Kirkorian, H.W. Ridlehuber, J.E. Desmond, G.H. Glover, J.D.E. Gabrieli, Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 14494–14499.
[129] M.R.M. Vianna, M. Alonso, H. Viola, J. Quevedo, F. de Paris, M. Furmna, M. Levi de Stein, J.H. Medina, I. Izquierdo, Role of hippocampal signaling pathways in long-term memory formation of a nonassociative learning task in the rat, Learn. Mem. 7 (2000) 333–340.
[130] B.E. Viets, A. Tousignant, M.A. Ewert, C.E. Nelson, D. Crews, Temperature-dependent sex determination in the leopard gecko, *Eublepharis macularius*, J. Exp. Zool. 265 (1993) 679–683.
[131] D. Viggiano, D. Vallone, H. Welzl, A.G. Sadile, The Naples high- and low-excitability rats: selective breeding, behavioral profile, morphometry, and molecular biology of the mesocortical dopamine system, Behav. Genet. 32 (2002) 315–333.
[132] J.S. Villarreal, F. Gonzalez-Lima, J. Berndt, E.J. Barea-Rodriguez, Water maze training in aged rats: effects on brain metabolic capacity and behavior, Brain Res. 939 (2002) 43–51.
[133] N.D. Volkow, G.-J. Wang, J.S. Fowlder, J. Logna, B. Angrist, R. Hitzemann, J. Lieberman, N. Pappas, Effects of methylphenidate on regional brain glucose metabolism in humans: relationship to dopamine D_2 receptors, Am. J. Psychiatry 154 (1997) 50–55.
[134] F.S. vom Saal, Variation in phenotype due to random intrauterine positioning of male and female fetuses in rodents, J. Reprod. Fertil. 62 (1981) 633–650.
[135] F.S. vom Saal, F.H. Bronson, Sexual characteristics of adult female mice are correlated with their blood testosterone levels during prenatal development, Science 208 (1980) 597–599.
[136] A. Vyas, R. Mitra, B.S. Shankaranarayana Rao, S. Chattarji, Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons, J. Neurosci. 22 (2002) 6810–6818.
[137] I.Q. Whishaw, C.H. Vanderwolf, Hippocampal EEG and behavior: changes in amplitude and frequency of RSA (theta rhythm) associated with spontaneous and learning movement patterns in rats and cats, Behav. Biol. 8 (1973) 461–484.
[138] S.J. Wiegand, E. Terasawa, W.E. Bridson, R.W. Goy, Effects of discrete lesions of preoptic and suprachiasmatic structures in the female rat, Neuroendocrinology 31 (1980) 147–157.
[139] M.T. Wong-Riley, Cytochrome oxidase: an endogenous metabolic marker for neuronal activity, Trends Neurosci. 12 (1989) 94–101.
[140] M. Wong-Riley, E.W. Carroll, Effect of impulse blockage on cytochrome oxidase activity in monkey visual system, Nature 307 (1984) 19–25.
[141] M.T. Wong-Riley, T.T. Norton, Histochemical localization of cytochrome oxidase activity in the visual system of the tree shrew: normal patterns and the effect of retinal impulse blockage, J. Comp. Neurol. 272 (1988) 562–578.
[142] M.T. Wong-Riley, C. Welt, Histochemical changes in cytochrome oxidase of cortical barrels after vibrissal removal in neonatal and adult mice, Proc. Natl. Acad. Sci. U. S. A. 77 (1980) 2333–2337.
[143] M.T. Wong-Riley, S.C. Tripathi, T.C. Trusk, D.A. Hoppe, Effect of retinal impulse blockage on cytochrome oxidase-rich zones in the macaque striate cortex: I. Quantitative electron-microscopic (EM) analysis of neurons, Vis. Neurosci. 2 (1989) 483–497.
[144] M.T. Wong-Riley, T.C. Trusk, S.C. Tripathi, D.A. Hoppe, Effect of retinal impulse blockage on cytochrome oxidase-rich zones in the macaque striate cortex: II. Quantitative electron-microscopic (EM) analysis of neuropil, Vis. Neurosci. 2 (1989) 499–514.
[145] M.T. Wong-Riley, M.A. Mullen, Z. Huang, C. Guyer, Brain cytochrome oxidase subunit complementary DNAs: isolation, subcloning, sequencing, light and electron microscopic in situ hybridization of transcripts, and regulation by neuronal activity, Neuroscience 76 (1997) 1035–1055.
[146] M.T.T. Wong-Riley, F. Nie, R.F. Hevner, S. Liu, Brain cytochrome oxidase: functional significance and biogenomic regulation in the CNS, in: F. Gonzalez-Lima (Ed.), Cytochrome Oxidase in Neuronal Metabolism and Alzheimer's Disease, Plenum Press, New York, 1998, pp. 1–53.
[147] M.T. Wong-Riley, Z. Huang, W. Liebl, F. Nie, H. Xu, C. Zhang, Neurochemical organization of the macaque retina: effect of TTX on levels and gene expression of cytochrome oxidase and nitric oxide synthase and on the immunoreactivity of Na^+K^+ ATPase and NMDA receptor subunit I, Vis. Res. 38 (1998) 1455–1477.
[148] M. Wong-Riley, B. Anderson, W. Liebl, Z. Huang, Neurochemical organization of the macaque striate cortex: correlation of cytochrome oxidase with Na^+K^+ ATPase, NADPH-diaphorase, nitric oxide synthase, and *N*-methyl-D-aspartate receptor subunit 1, Neuroscience 83 (1998) 1025–1045.
[149] M. Wong-Riley, A. Guo, N.J. Bachman, M.I. Lomax, Human *COX6A1* gene: promoter analysis, cDNA isolation and expression in the monkey brain, Gene 247 (2000) 63–75.
[150] P. Yahr, Neural circuitry for the hormonal control of male sexual behavior, in: P.E. Micevych, R.P. Hammer (Eds.), Neurobiological Effects of Sex Steroid Hormones, Cambridge University Press, Cambridge, 1995, pp. 40–56.
[151] C. Zhang, M. Wong-Riley, Expression and regulation of NMDA receptor subunit R1 and nitric oxide synthase in cortical neuronal cultures: correlation with cytochrome oxidase, J. Neurocytol. 28 (1999) 525–539.
[152] C. Zhang, M.T. Wong-Riley, Synthesis and degradation of cytochrome oxidase subunit mRNAs in neurons: differential bigenomic regulation by neural activity, J. Neurosci. Res. 60 (2000) 338–344.
[153] C. Zhang, M.T. Wong-Riley, Depolarizing stimulation upregulates GA-binding protein in neurons: a transcription factor involved in bigenomic expression of cytochrome oxidase subunits, Eur. J. Neurosci. 12 (2000) 1013–1023.