

## B - Behaviour

## UNDERSTANDING HOW DOGS LEARN: IMPORTANCE IN TRAINING AND BEHAVIOR MODIFICATION

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### Introduction

Behavior modification is nothing more than the process of altering an animal's behavior. This discussion addresses how learning affects the overall phenotype, how the effects of the gross environment interact with the phenotypes, and how environmental effects at all mechanistic levels contribute to secondary changes in the phenotype.

The classic client and veterinarian response to having "behavior mod" recommended as part of a treatment plan is to exclaim that they "**don't have time for that**". What is not understood here is that we engage in behavior modification either actively or passively every hour of the day and in everything we do. The basic tenets of behavior modification treatment are not complex, and are put into action whether or not we consciously acknowledge or recognize that this is so. Accordingly, clients are often unconsciously and accidentally employing principles associated with learning and behavior mod, and inadvertently doing an excellent job of reinforcing the behaviors about which they are most distressed!! Our focus should be to help clients understand that learning occurs all the time and that we can shape the direction, rate, and complexity of the learning process with conscious effort. This does **not** mean that the clients 'must' engage in complex active behavior mod. It **does** mean that they can use small, relatively passive techniques to effect huge changes.

The problem with changing any behavior is 2 fold: (1) inertia is a powerful force, and (2) breaking behaviors down into elements that require change and understanding how to change them can be difficult to do. This difficulty lies in understanding exactly what is called for in the behavior modification technique of choice and

in the timing of the client's response to the dog's behavior and communicatory gestures. Before any client can change any animal's behavior - or their own - they **MUST** recognize (1) what normal signaling is, (2) what signals are associated with the problem they wish to change, and (3) what signals precede #2. Two examples will help make this clear.

### Human example

Eating is a normal mammalian behavior. Propensity to gain weight is an adaptive strategy dating to human prehistory; weight gain acted as a safe-guard to get humans through times of severe resource restriction. In fact, although the hormone leptin regulates fat, it actually acts to maintain some level of function in fat cells. Overeating - when out-of-context to the resource environment - leads to obesity. If people want to lose weight they have to change their behavior. Accordingly, by recognizing when their behaviors have stepped over the line from normal, contextual eating in response to hunger and future expectations of resource environments to out-of-context overeating, people have satisfied conditions 1 and 2 above. If they wish to intervene to stop the cycle they need to recognize the behaviors that precede condition 2. If the condition that precedes a trip to the refrigerator is a TV commercial about food, the obvious answer is - in the context of risk assessment where full information is not available - to back away from the television set as soon as any commercial begins. If it's the act of watching TV and anticipating the commercial and food breaks that is associated with over-eating, removing the TV from the equation can help.

### Canine example

Barking is a normal canine behavior, but not

all barking is the same. Alerting barks have an increasing tone and occasionally elements of a howl. Barks signaling distress are often sharp, high-pitched, repetitive, and relatively atonal. If a dog is affected with separation anxiety and the non-specific sign associated with the condition is barking, the client must recognize how their dog's bark deviates from 'normal'. In this example we have satisfied conditions 1 and 2, above. If the client wishes to intervene to change the behavior that results in the barking, it is best to intervene before the bark. This means that they have to recognize behaviors that signal the target non-specific sign is likely to occur.....this is a form of risk assessment and if clients understand behavior mod in these terms they will find it very easy to intervene at the appropriate time. In this example, the dog starts to pace and pant while the client is still at home, and the barking only occurs once they have left. Accordingly, the best time to intervene to alter the barking, is when the dog begins to pace and pant, satisfying the 3<sup>rd</sup> condition, above. If the client is serious about ablating all anxiety, they have to intervene in the behaviors that precede the panting and pacing. If these behaviors are also preceded by other anxious behaviors, the client must intervene in the behaviors that precede **those** anxious behaviors, and so on. This is the behavior modification version of 'it's turtles all the way down'.

These are the patterns clients have to recognize to appropriately intervene in order to accomplish 'behavior mod'.

In the examples and discussion above the clients are to 'intervene', but intervention is deliberately left undefined. In any situation there are three environments available for intervention which can be potentially modified: the physical environment, the behavioral environment, and the pharmacological environment. These environments are not independent. The key to understanding how dogs learn is to appreciate the complexity of interaction between these environments, and the importance of factors affecting temporal and intensity changes and interactions within these environments.

#### Basic concepts pertaining to environmental effects at the gross or systems level

The physical environment includes perceived and actual space considerations, any visual, olfactory, or auditory stimuli, other animals, relevant objects such as litter boxes, and any devices that might change an animal's perception, such as gauze curtains, fences, or the presence of background music.

While other animate objects may be part of the physical environment, they may potentially also

interact within the behavioral environment. This is not requisite and certainly the mere presence of a dog that can be seen through a window may be sufficient stimulus for an inappropriate behavior although that dog may never be an active participant in any behavioral interaction. Conversely, because of the neurochemical changes that may be induced, the olfactory cues in the physical environment may directly or indirectly alter the behavioral environment.

Because perception is so critical in the evaluation of the physical environment it must be remembered that this includes the time environment or the schedules of the clients. Some problems, like separation anxiety in dogs, may develop when the only environmental change is one of time: day length shortens or the clients schedules change. Part of any treatment plan must address this environmental change. The physical environment may be modified because it is a direct part of the problem, for example, insufficient space for exercise, or because changing the physical environment can help solve the problem, for example by providing dog houses to give each dog personal space in an unshared rain shelter.

The behavioral environment focuses on behavior modification, rather than on the alteration of the perceptual or tangible environmental component. The behavioral environment includes the individual and the social environment of anyone (human or animal) with whom the individual might interact. If there is another social group with whom the individual doesn't interact, but whose social interaction affects the individual (i.e.: a group of cats whose play affects the resident dog, but who don't interact with him directly), this is also a component of the behavioral environment. In the example just used, if the dog barks every time the cats roughhouse, part of the treatment may be to teach the cats to play elsewhere or to not play in so rough a manner.

The third environment that can be modified may, in fact, be the most subtle one: the pharmacologic environment. The pharmacologic environment has two components: the endogenous environment and the exogenous environment. We used to think that these could be nicely separated. Given what we now know about how drugs work to affect memory at the cellular and molecular level, and given the role of anti-anxiety medication on indirectly affecting corticosteroids.....caution is urged in blind faith acceptance of **any** simplistic paradigm.

The endogenous or internal pharmacological environment is influenced by sex hormones and other physiological parameters. Effects can be the result of neutering, in the case of sex hormones, and disease, in the case of most physiological

parameters (including those associated with gonads). It's important that we acknowledge the role of either primary or secondary physical illness because there is a tendency to forget that an animal's behavior can change with physiological changes attendant with aging or illness. Endogenous changes in pharmacological environments affect the manner in which the animal interacts in the behavioral and physical environments. Because the exogenous pharmacological environment includes pharmacological intervention (drug therapy), we have further effects on learning, metabolism of brain chemistry, and re-regulation of physiological pathways involved in stress and distress.

When we castrate a dog we remove most of the circulating testosterone (castration results in an androgen drop within 6 hours; the bulk of the hormonal decrease is complete in 72 hours); however, this, alone, is unlike to wholly 'fix' any true behavior problems. Testosterone, like most androgens, acts as a behavioral modulator that may facilitate the attainment and escalation of the aggressive state. If a dog is already aggressive, the difference between it in the neutered and un-neutered form will be one of degree. The intact dog will react more easily, escalate more quickly and plateau at a higher level of aggressive intensity, will become less reactive more slowly, and may even remain poised for the next bout more easily since they main return to a higher state of vigilance post-aggressive event than at which they started prior to the aggressive event. Other dimorphic behaviors associated with the presence of testosterone include urine marking with lifted leg, roaming, and some types of mounting. Castration results in a 90% decrease in roaming in male dogs that roamed prior to castration, a 75% reduction in male-male aggression, a minimal 60% in urine marking, and an 80% reduction in mounting (Hart 1974; Hopkins et al., 1976). Marking, mounting, and, to a lesser extent because of the modulator effect discussed above, fighting, are complex behaviors not wholly controlled by only hormones. There is a huge learning component to these behaviors that people neglect to acknowledge. If marking has been ongoing for some time, castration, alone, will not ablate it, but may decrease it. The part of the behavior that is a learned response remains in the absence of deliberation modification to alter it. The same logic holds for mounting.

Less attention has been paid to the role of female sex hormones and aggressive behavior. There may be a role for female hormones, but it appears to be less direct than for male hormone. Female puppies that were *already* showing aggressive tendencies at the time of spaying may be rendered

worse by the procedure (O'Farrell and Peachey, 1990). This may be either a direct effect of *in utero* androgenization or an indirect effect of decreased feminization effects due to a lack of female hormones (Overall, 1995). Female dogs affected by impulse control aggression appear phenotypically and neurochemically different from males, and tend to have an age on onset that is statistically significantly younger than do male dogs diagnoses with the same condition (Overall, et al., unpublished).

As a final cautionary word about over-emphasis of the endogenous pharmacological environment in the etiology and causality of behavioral problems it is important to note that most aggression is a social, not a hormonal, condition. Certainly hormones can act as modulators. Accordingly, work continues on the effects of thyroid hormones, and those associated with the hypothalamic-pituitary-adrenal axis. Expect elegant complexity.

Still, it's important to remember that none of the three environments mentioned above is independent: they all interact. A perturbation in one environment can cause a shift in another. Furthermore, all of these environments have system and cellular / molecular effects which, in turn, interact. This is difficult to understand because it's complex, and because of that complexity we actually know very little about how any part of the system really works.

### Principles of Behavior Modification

Behavior modification utilizes six main learning tactics or paradigms: habituation, extinction, desensitization, counter-conditioning, flooding, and avoidance/aversive conditioning. Within this structure, 3 other concepts are important: learning, overlearning, and reinforcement.

Before discussing the 6 main tactics, we need to understand what is meant by learning. Learning is generally defined as the acquisition of information or behavior through exposure and repetition. At the cellular and molecular level learning is defined as cellular and receptor changes that are result of stimulation of neurons and the manufacture of new proteins. It is these new proteins / receptors, that then change the way the cell responds when next stimulated. It's important to remember that no cell / neuron acts on its own: region of the brain, neurochemical tract, and interactions with other cells are critical for determining response.

Overlearning is a technique often used by performers and athletes when the specific behavior desired is obtained through such consistent practice (read, repeated stimulation of the same cells in the same pathways) that the response becomes almost automatic or a 'gestalt',

requiring little conscious thought (read, encoded genetically through new protein receptors). We need to remember that we can overlearn good behaviors, but that undesirable behaviors can also be perfectly elicited via overlearning (eg, the dog jumps up on you whenever he sees you because you pet him - the entire sequence of alerting, moving, and elevating is now a flawless, unconscious response).

Reinforcement is also key if we are to successfully employ the basic tactics of behavior modification. Reinforcement can either be positive, encouraging repetition of the behavior, or negative, discouraging the repetition of the behavior. Negative reinforcement discourages the behavior because the animal is rewarded with a more favorable experience not just when they cease the undesirable behavior, but as a **result of ceasing it**. It's important to realize that negative reinforcement is completely different from punishment where no reward structure is in place.

These distinctions and definition are particularly important when we consider learning at the cellular and molecular level because LTP can take place in different regions. Fear primarily involves the amygdala, whereas various 'reward' systems involve parts of the cortex, the substantia nigra, and miscellaneous parts of the 'limbic system'. In addition to regional activity, positive reinforcement, negative reinforcement, and punishment primarily use different neurochemical tracts or way-stations. Positive reinforcement uses opiate and dopaminergic systems, punishment involves the flight, freeze, or fight pathways of the norepinephrinergic sympathetic systems, and negative reinforcement likely involves some complex association of both of these, plus the serotonergic system. It's important to acknowledge that these neuroanatomical and neurochemical associations are understood poorly, at best, and that generalizations about them are painted in the broadest possible strokes.

#### Definitions of behavior modification tactics

**1. Habituation** is the *normal attenuation* of a response to something novel in the environment that is attendant with an increase in intensity or frequency of exposure to the stimulus in circumstances where nothing horrendous happens. For example, a doorbell may startle a new puppy, but as she hears it more frequently in a benign context she may habituate to it (if inappropriately reinforced, she may not habituate to it...instead she may develop a learned response that gets her attention). People who move from the city to the country habituate to bird songs and insect calls.

**2. Extinction** is the process by which normal or

conditioned responses are decreased or attenuated by exposure to a stimulus that elicits the response in the *absence* of the reward. The new puppy that barks at the doorbell may get inappropriately reinforced by well-meaning clients who pick her up and reassure her. They are actually, and usually unintentionally, rewarding her for barking, so she continues to bark when the doorbell rings. This is now a conditioned response. If they consistently ignore her they will extinguish the response (if the sound of her own bark has not become self-reinforcing). Caution is urged since resistance to extinction is a very common phenomenon and occurs with very little reinforcement. The classic introductory psychology course story about this usually involves an elevator that is broken more often than not. Still, because it operates 1/10 or 1/20 times, most people walk into the lobby and push the button on the off chance that the elevator is working. The higher the destination floor, the more likely people are to push the button because the 'reward' is greater, albeit rare. The people in this example are exhibiting resistance to extinction due to an intermittent reinforcement schedule.

**3. Desensitization** is a decrement in response that is produced by gradual exposure to a stimulus that elicits the response. If the puppy used above has become fearful of or stimulated by the doorbell, her bark, or the events occurring around the ringing of the doorbell, using a tape recording or the doorbell could help her stop the undesired response. If the tape is played very softly at first so that she doesn't react and then only gradually increased in volume at increments designed to elicit no response, she may become desensitized to the doorbell.

**4. In counter-conditioning**, negative or undesirable behavior is extinguished or controlled by teaching the animal to do another behavior (preferably favorable and fun) that *competitively interferes* with the execution of the undesirable behavior. This is best coupled with desensitization. Again, using the puppy above, she will learn faster if she is first taught to sit and stay and relax (the key here) in exchange for a treat. She must be absolutely quiet and calm, and convey by the look in her eyes, her body posture, and her facial expressions that she would do anything for her client. Calm and lack of anxiety and calmness are helpful because we know that hormones associated with stress and anxiety - corticosteroids - impede the ability to learn complex associations (Yau et al., 2002). This is key to understanding newer approaches (Overall, 1997) to behavior modification.

Once the puppy can do relax and attend to her person for exercises lasting a half hour or so,



true desensitization begins: the tape recording is gradually increased in volume, always at a level below that which provokes anything but a transient response in the dog. Performing the adoration act for a food salary (counter-conditioning) is incompatible with or competitively exclusive of barking. If at any point the puppy starts to act anxious or to not attend to her client, the tape recording should be lowered in volume until she can relax again. This is the key here - the sitting and staying is merely a facilitator for the relaxation response. There is no sense to having the dog sit and stay if it is panting, salivating, its pupils are dilated, its ears are back, and it is clearly distressed. What on earth is the dog learning? It's simple - the dog is learning to be more distressed and also teaching his- or herself to become refractory to complex learning because of arousal of the HPA-axis (hypothalamic-pituitary-adrenal axis). This is why simple 'sit-stay' programs (Voith, 1982) so often fail: the dog sits, but is still distressed.

*The gestalt of relaxation is the first step to changing the behavior.* Counter-conditioning coupled with desensitization is an extremely time consuming technique. It means that one must constantly go back and repeat the exercises where there was a lesser response until there is none, and it means that one must attend to all the patient's communicatory signals. It is hard work, but it does work. Clients who are least successful with this technique want both quicker fixes and less work. Disabuse them of the possibility of either at the outset. Clients also want their dogs to be "quick", "fast learners", "A+ students", "achievers". These are all words that I have heard clients use as they whip through the counter-conditioning and desensitization exercises so quickly as to **provoke** anxiety in the dog. Such client behavior and neediness sabotages the program.

Problem dogs have special needs. These needs do not reflect on the intelligence of the dog, nor on the abilities of the clients. These dogs can eventually be A+ students, but they will have to take a longer, harder path, and although the client did not cause the dog's behavioral problems, they are constrained to accompany the dog on that path if the dog is to get better. That said, the clients should be able to give themselves permission to break any behavior mod program into 5 minute blocks, that they can practice when they can find the time. If clients feel they can succeed, they will at least try. If the instructions are ones that the client cannot integrate with their lifestyle, they will not try, or they will fail. Most of us can find 5 minutes multiple times a day, but we'd have trouble finding an uncommitted ½ hour.

**5. Flooding** involves prolonged exposure at a level that *provokes* the response so that the animal eventually gives up. This exactly the opposite of the approach taken in desensitization. **It is far more stressful than any of the other therapy strategies and, used inappropriately - which it usually is - could damage the animal.** If nothing else works for the puppy, flooding would involve enclosing her in a small space (a crate or small room) and constantly playing a tape of a doorbell louder than it is until she ceases to bark. She cannot be disturbed until this happens and that could take a while. Caution is urged: if the dog's anxiety level continues to worsen **you are at risk of creating a tremulous, fearful, or likely panicked dog.** In most cases - except those involving minor fears where physiological and behavioral responses can be easily monitored - flooding is a last resort and should always be executed as humanely as possible. Furthermore, no client should try this without discussing the technique and its applicability to the situation with someone who understands learning.

**6. Avoidance or aversive conditioning** [eg, punishment] involves the presentation of an aversive stimulus in response to an inappropriate or undesirable behavior; the stimulus is intended to *abort* the behavior and to *decrease the probability* of it occurring in the future. This is the correct definition of punishment. To be most successful the stimulus designed to abort the behavior must occur as early as possible but certainly within the first 30-60 seconds of the **onset** of the behavioral **sequence** (within tenths of a second of the exhibition of the actual undesirable behavior) and must be consistent and appropriate.

The critical factors in punishment include:

1. timing;
2. consistency,
3. appropriate intensity, and
4. the presence of a conditioned response.

Point 4, the presence of a conditioned response, means that when the undesirable behavior ceases there has to be some favorable stimulus or reward that the dog gets even it is just praise or a pat.

**This is the single most frequently ignored part of treatment** for pets with behavioral problems: when these pet are not causing trouble almost no one tells them how good they are. Instead, when they are quiet, the clients ignore them, possibly because they welcome this fragment of serenity so greatly. Unfortunately, this is also where the most ground is lost. If the pup is sleeping, you don't have to jump up and down and arouse him to reward him. Rewards can be calm, quiet, and passive. Instead when the puppy is sleeping, gently and s-l-o-w-l-y say, in a low, calm,

soothing tone, 'what a g-o-o-d boy'. If the client MUST touch the dog, they must do so by pressing with long, slow, firm, strokes. No one should pet or agitate the dog when the dog is quiet, if 'quiet' is the response they hope to reinforce.

To reiterate, it is important to emphasize to clients that - if it is to work - punishment must be as closely coupled with the inappropriate event as possible, must startle - without terrifying - the animal to the point where they just abort the behavior, must be appropriate in duration and intensity (it is never appropriate to beat a dog senseless, yet people tend to continue all forms of punishment way after the abortion of the event has occurred), and that all of this must occur in a consistent manner that incorporated aborting the inappropriate behavior every time the undesirable behavior occurs. The latter is the reason why dogs often appear 'resistant' to learning to stay off the furniture: no one yells at them when they sleep if they are home alone. The sofa dog is experiencing an intermittent reward schedule. The best way to maintain a behavior is to use an intermittent reward schedule. This dog has learned that she can sometimes sleep on the sofa - all we are negotiating is the definition of 'sometimes'.

Aversive conditioning may be best used early in the development of the undesirable behavior. Early warning signs of most aggressions are recognizable if the client learns for what to look. As emphasized above, in order for punishment to succeed it has to occur preferably in one second, but generally within the first 30-60 seconds, of the *onset* of the inappropriate behavioral sequence.....hidden in this phrase is the truism that if the client learns to recognize precursor behaviors, they will have far more success in intervening at the appropriate time and 'correcting' the undesirable behavior. The punishment should preferably startle the animal sufficiently **only** to interrupt the behavior and abort any attempt at immediate resumption. The pup can then be taught a more appropriate behavior, such as sitting and staying. Sitting here serves as a 'time out' for both handler and pup, while employing a behavior that both species recognize as a deferential one (sitting). Done correctly, the pup learns that the human is reliable and trustworthy and that he or she can take all cues as to the appropriateness of his or her behavior from the client. This is a key point, because at the crux of behavioral problems is the fact that these dogs are abnormal; therefore, they are incapable of making appropriate, in-context distinctions. These dogs exhibit inappropriate, out-of-context behavior. Early intervention must be aimed at getting the dog to trust the client

(excellent voice 'control') and teaching him or her to make better context distinctions by taking cues about the appropriateness of the behavior from the client.

Finally, the best success with any aversive paradigm is obtained if, as soon as the animal stops the undesirable behavior they are given a clear cue about what is expected and what the reward will be. **If people cannot or will not do the entire sequence appropriately, they have absolutely no business using any form of punishment. Really, what they are doing in the absence of full follow-through is abuse.**

People usually resort to physical punishment as the correction method of choice when what they have tried fails, or because this is how they, themselves, were raised and no one taught them differently. If clients cannot or do not believe that they can learn to change, there is no hope for the dog's behaviors to change. Conversely, by learning to treat a dog more humanely thank you, yourself, were treated, you can become a better person.

Notice that no where is it written that punishment must be physical. Furthermore, doing punishment well is just as hard work as is appropriately executed counter-conditioning and desensitization. Punishment is never an easy out and has a high probability of backfiring unless the client understands that its focus is to decrease the probability of future inappropriate events.

### Reward Structures

It's important to understand reward structures and what these mean at the cellular and molecular level for behavior modification. Behaviors are reinforced or learned best if every time they occur they are rewarded. At the cellular level, repeated reinforcement insures better, more numerous, and more efficient connections between neurons (Carter et al., 2002; Wittenberg and Tsien, 2002). Stimulation is induced when a neurochemical in a synapse triggers a receptor to engage it. This stimulation of the receptor engages second messenger systems in the post-synaptic cell, usually cAMP. The result is cellular memory or long-term potentiation (LTP). By itself, this initial process represents E-LTP or 'early phase LTP' and STM (short-term memory). The process is short-lasting, RNA and protein-synthesis-independent, and the result does not persist or become self-potentiating unless the stimulus is consolidated into L-LTP 'late phase LTP', which is a more permanent form (Schafe et al., 2001). E-LTP can be induced by a single train of stimuli in either the hippocampus or the lateral amygdala. In contrast, L-LTP and LTM (long-term memory) requires repeated stimulation of cAMP, induction

of cAMP response element binding protein (CREB - a nuclear transcription factor), and is long-lasting, protein synthesis dependent, and is RNA transcription dependent (Schafe et al., 2001). When stimulation continues, BDNF enhances neurotransmission and potentiates what is called activity-dependent plasticity at synapses (eg, learning), particularly in the region of the brain most involved in learning, the hippocampus. This effect can also occur in the lateral amygdala and is one modality postulated to be involved in learned or conditioned contextual fear (Schafe et al., 2001).

This neurobiology is important to consider in the context of reward systems. It explains why continuous reward works best in acquiring a behavior (E-LTP and STM) and why intermittent reward acts best to maintain a learned behavior (L-LTP and LTM). This neurobiology explains why a really excellent reward (jackpot) can help you learn or reinforce a behavior quickly and why a really horrible experience can stimulate the amygdala to encode learned panic or phobia molecular - consider neuromolecular biology of these (inability to escape from flooding). The amygdala, itself, is an incredibly complex few mm<sup>3</sup>. Almost all outgoing tracts that control some higher forms of integration of behavior in the cerebral cortex, hypothalamus, brain stem et cetera have their efferents shaped by the location of their origin in the amygdala (Davis, 1997). Additionally, the lateral amygdala is likely the site where memories of conditioned (learned) fear are created through a process involving neuronal plasticity (Schafe et al., 2001). In fact, if one lesions or inactivates the lateral amygdala, it is impossible to either acquire a fear or to express a previously acquired fear (LeDoux et al., 1990).

When one considers rewards - or aversive stimuli - which best induce these quick learning experiences, it is important to consider them in terms of their evolutionary value. Evolutionarily tightly coupled rewards - ones that selection has shaped to be of particularly high value - are those directly coupled to survival: food, freedom, elimination, mating. Evolutionarily less tightly coupled rewards - ones on which survival should not hinge - will be of lesser value: praise, play. When one considers the molecular biology of learning within the evolutionary context of very pleasurable or very fearful stimuli, it should be clear how behaviors can best be modified.

**So what does this mean for very early learning - before there are problems (eg, 'socialization')?**

Pups who stay with breeders for extended periods of time (3-4 months of age) without exposure to

novel circumstances and individuals, may never respond appropriately to them. If these pups are exposed to many people, dogs, and new experiences, even if they stay with the breeder for an extended period, the benefit of exposure should generalize to strangers and changing environments. This is probably some of the logic for taking puppies crated to dog shows. The problematic situation associated with lack of exposure appears to be more common in kennel pups. When adopted these pups may exhibit fear of all new, non-kennel environments. This fear can be so crippling that these dogs are unable to go in and out of the house or walk on the street. With behavior modification and pharmacological intervention these dogs can improve, but are probably never normal. Pups who are kept in kennels beyond 14 weeks of age are likely to never be normal, and will exhibit timidity and a lack of confidence (Pfaffenberger and Scott, 1959). Accordingly, pups who are brought home at 8 weeks of age and kept inside with one or a few humans, may also find it difficult to make the transition to other environments.

It is clear from the above that the best time to recommend that a client adopt a pup is about 8.5 weeks of age. At this time pups are ready to be house-trained - this is the first time they can cognitively make the connections important for substrate preferences and stimulation for elimination **and**, concurrently, volitionally inhibit elimination - and are optimally poised to benefit from exposure to all 'socialization' environments. There are two caveats to this rule of thumb. Later age is acceptable if the dog is going to be exposed to lots of different people, instead of just one person, at the breeder's. Furthermore, if house-training is important to the future client, the breeder should start this process if the pup remains with them. The preceding discussion about LTP should make it clear why it is also so hard to 'unlearn' something. Getting it right at the beginning is most helpful. Remember that pups learn from novel experiences at this age, so the adoption process should not be scary, painful, or associated with horrific circumstances such as traumatic shipping, mutilation, tattooing, or punishment (think - LTP in the lateral amygdala.... and now you have 'encoded' fear!). Although observance and understanding of the appropriate periods is no guarantee that future problems will not develop, the client will be able to minimize the risk that future problems are due to lack of exposure during these periods.

It is important to appreciate that some of the effects of developmental/sensitive periods (Bateson, 1979) may be mitigated by the personality of the individual puppy - not to mention the breed

- and by the intensity of attention that the animal receives. The extent to which mitigation of the effects of lack of exposure in early life is possible is unclear. Certainly, the one situation where people have definitely caused the aggressive problem result not from lack of exposure, but from inappropriate exposure: abuse. Dogs that are abused may become fearful, fearfully aggressive, or outright aggressive. Which path is taken may have less to do with the form of the abuse than with the underlying personality of the dog. Gene x environment interactions are well understood only for rigidly controlled, experimental situations. This does not describes dogs.

#### Exogenous pharmacological environments (drugs): Roles for neuronal stimulation, synaptic plasticity, and receptor protein transcription and translation

The best drugs to help treat behavioral conditions are the tricyclic antidepressants (TCAs) and the selective serotonin re-uptake inhibitors (SSRIs). These 2 classes of drugs and their descendants have made the use of broad-acting compounds like progestins, tranquilizers, sedatives, and anti-convulsants, at best, anachronistic. What makes TCAs and SSRIs special and why are they so useful for anxiety disorders? The key to the success of these drugs is that they utilize the same second messenger systems and transcription pathways that are used to develop cellular memory or to "learn" something. This pathway involves cAMP, cytosolic response element binding protein (CREB), brain derived neurotrophic factor (BDNF), NMDA receptors, protein tyrosine kinases (PTK) - particularly Src - which regulate activity of NMDA receptors and other ion channels and mediates the induction of LTP (long-term potentiation = synaptic plasticity) in the CA1 region of the hippocampus (Daniel et al., 1998; Salter, 1998; Trotti *et al.*, 1998).

#### There are two phases of TCA and SSRI treatment

Short-term effects and long-term effects. Short-term effects result in a synaptic increase of the relevant monoamine associated with re-uptake inhibition. The somatodendritic autoreceptor of the pre-synaptic neuron decreases the firing rate of that cell as a homeostatic response. Regardless, there is increased saturation of the post-synaptic receptors resulting in stimulation of the  $\alpha$ -adrenergic coupled cAMP system. cAMP leads to an increase in PTK as the first step in the long-term effects. PTK translocates into the nucleus of the post-synaptic cell where it increases CREB, which has been postulated to be the post-receptor target for these drugs. Increases in CREB lead

to increases in BDNF and tyrosine kinases (e.g., trkB) which then stimulate mRNA transcription of new receptor proteins. The altered conformation of the post-synaptic receptors renders serotonin stimulation and signal transduction more efficient (Duman, 1998; Duman *et al.*, 1997).

This should sound an awful lot like how learning occurs at the molecular level through LTP - because it is. Simply, TCAs and SSRIs work so well because they stimulate the neurochemicals involved in anxiety-related pathways, and because they augment the rate at which learning occurs because of the parallel effect on pathways and mechanisms involved in learning.

Knowledge of the molecular basis for the action of these drugs can aid in choosing treatment protocols. For example, the pre-synaptic somatodendritic autoreceptor is blocked by pindolol (a  $\beta$ -adrenoreceptor antagonist) so augmentation of TCA and SSRI treatment with pindolol can accelerate treatment onset. Long-term treatment, particularly with the more specific TCAs (e.g., clomipramine) and SSRIs, employs the same pathway used in LTP to alter reception function and structure through transcriptional and translational alterations in receptor protein. This can be thought of as a form of in vivo "gene therapy" that works to augment neurotransmitter levels and production thereby making the neuron and the interactions between neurons more coordinated and efficient. In some patients short-term treatment appears to be sufficient to produce continued "normal" functioning of the neurotransmitter system. That there are some patients who require life-long treatment suggests that the effect of the drugs is reversible in some patients, further illustrating the underlying heterogeneity of the patient population considered to have the same diagnosis.

#### Monitoring

Monitoring of side-effects is critical for any practitioner dispensing behavioural medication. The first tier of this involves the same tests mandated in the pre-medication physical and laboratory evaluation. Age-related changes in hepatic mass, function, blood flow, plasma drug binding, et cetera cause a decrease in clearance of some TCAs, so it is prudent to monitor hepatic and renal enzymes annually in younger animals, biannually in older, and always as warranted by clinical signs. Adjustment in drug dosages may be necessary with age.

It is preferable to withdraw most patients from one class of drug before starting another. For changing between SSRIs and MAOIs the recommended drug-free time in humans and dogs is two weeks (2 + half-lives: the general rule of thumb for



withdrawal of any drug). SSRIs can be added to TCAs and may then exhibit a faster onset of action than when they are given alone. This is due to the shared molecular effects on second messenger systems of both TCAs and SSRIs. Combination treatment allows the clinician to use the lower end of the dosage for both compounds which minimizes side effects while maximizing efficacy. Furthermore, benzodiazepines can be used to blunt or prevent acute anxiety-related outbursts on an as needed basis in patients for whom daily treatment with a TCA or an SSRI is ongoing. Together, the combination of benzodiazepines and TCAs / SSRIs may hasten improvement and prevent acute anxiety-provoking stimuli from interfering with treatment of more regularly occurring anxieties.

When stopping a drug, weaning is preferred to stopping abruptly. Weaning minimizes potential central withdrawal signs, and allows determination of the lowest dosage that is still effective (Overall, 1997, 1999a, 2000). Long-term treatment may be the rule with many of these medications and conditions, but maintenance may be at a considerably lower level of drug than was prescribed at the outset. The only way the practitioner will discover if this is so is to withdraw the medication slowly.

### Factors Affecting the Success of Treatment

Five main factors contribute to the success of treatment. These are: client compliance, age of onset, predictability of outbursts, duration of the condition, and the pattern of the behavioral changes in response to environmental, behavioral, and pharmacological intervention. Of these, client compliance may be the most critical. Clients need to truly understand - in their gut as well as in their head - what is necessary to help their pet change and improve his or her behavior. The remaining factors are related. The younger the animal was when the problem started, the less predictable the outbursts, the longer the condition has been present, and the more frequent and intense the rate and extent of the outbursts, the worse the prognosis. Part of the reason for this is because the degree to which the inappropriate behavior has been learned increases with the changes stated for these parameters. The ability of the client to recognize the potential for a problematic event and to abort it before it happens cannot be over-emphasized. Clients sincerely committed to treatment learn to do this wonderfully.

### Words for future thought

The paradigmatic approach described above is incomplete and may be largely wrong. The study of behavior was left until last because

the brain is complex, and we don't know much. We know that the acquisition of a preferred behavior or a fear is dependent on the genetic and developmental template or response surface of the individual animal. With dogs, the story is even more complex. The story of dogs is the story of work, and in their shared co-evolutionary history with humans, dog breeds developed along the lines of particular job descriptions. Hence, the response surfaces for one breed may not be those for another, and the way dogs learn, may not be the same for all dogs.

So what is behavior modification, specifically?: Behavior modification is nothing more than the process of altering an animal's behavior. The classic client and veterinarian response to having "behavior mod" recommended as part of a treatment plan is to exclaim that they "don't have time for that". What is not understood here is that we engage in behavior modification either actively or passively every hour of the day and in everything we do. The basic tenets of behavior modification treatment are not complex, and are put into action whether or not we consciously acknowledge or recognize that this is so. Accordingly, clients are often unconsciously and accidentally employing principles associated with learning and behavior mod, and inadvertently doing an excellent job of reinforcing the behaviors about which they are most distressed!! Our focus should be to help clients understand that learning occurs all the time and that we can shape the direction, rate, and complexity of the learning process with conscious effort. This does not mean that the clients 'must' engage in complex active behavior mod. It does mean that they can use small, relatively passive techniques to effect huge changes.

Client fears: People are also afraid of the terms used in behavior mod: desensitization, counter-conditioning, conditioned stimulus, et cetera. These are jargon - anyone who is competent can teach clients to change their pets' behaviors without having to resort to these terms, and while implementing the concepts. The key to clear communication is to lose the jargon and concentrate on content.

Potential problems: The problem with changing any behavior is 2 fold: (1) inertia is a powerful force, and (2) breaking behaviors down into elements that require change and understanding how to change them can be difficult to do. This difficulty lies in understanding exactly what is called for in the behavior modification technique of choice and in the timing of the client's response to the dog's behavior and communicatory gestures. Before any client can change any animal's behavior - or their own - they MUST recognize (1) what normal signaling

is (Overall, 1997), (2) what signals are associated with the problem they wish to change, and (3) what signals precede # 2.

Although we ask clients to 'intervene' and - minimally - interrupt the behavior in step (3), intervention is deliberately left undefined. In any situation there are three environments available for intervention which can be potentially modified: the physical environment, the behavioral environment, and the pharmacological environment. These environments are not independent. The key to understanding how dogs learn is to appreciate the complexity of interaction between these environments, and the importance of factors affecting temporal and intensity changes and interactions within these environments.

### Keys to success

Keys to successful implementation of behavior modification include the following (Overall, 2003):

- (1) The clients must cease their own exhibition of any behaviors or behavioral sequences that promote, trigger, cause, encourage, or correlate with any of the behaviors in the dog or cat that they wish to change.
- (2) The clients must commit to clear signaling and a humane and possible set of rules by which they can interact with the cat or dog.
- (3) The signals in (2) must have a canine or feline equivalent so that the dog or cat both can understand and have the mental space to understand what the client wants. For example, sitting in dogs and cats is a 'stop' behavior, and in dogs this is a deferential behavior that functionally passes the job of giving the next signal back to the individual who engendered the 'sit'.
- (4) The behavior mod - which is a true rule structure - should be sufficient either signal to the dog or cat what they can expect to happen next or to teach them that they can look to the client for all cues about the appropriateness of their behavior if they are concerned.
- (5) The reward structure - which is another rule structure - should be clearly defined and appropriately reinforced at all times. Clients need to understand at their gut level that we teach best by rewarding every instance of appropriate behavior and that we retain what we have learned best by rewarding intermittently. Clients also need to understand that intermittent is NOT synonymous with 'seldom'.
- (6) Unless the client's intent is to teach the dog or cat to fear them, to teach the pet what will only engender dissatisfaction, or to confuse the pet,

clients MUST stop all punishment, shrieking, yelling, throwing things, et cetera, no matter how good it feels to them.

Important points about behavior mod that should go without saying, but don't: The following important points regarding behavior modification exercises are those which are most frequently misunderstood by clients and vets, alike.

1. Behavior modification exercises are NOT, repeat NOT, obedience exercises. At the very outset clients should be disabused of the notion that this is fancy obedience.

First, while sitting is part of obedience training, the goal of these programs is not just to have the dog sit, but to relax and be receptive to changing his or her behavior while doing so. It is critical that clients understand and appreciate this difference. Dogs that are stressed or anxious cannot successfully learn a more appropriate behavior and they certainly cannot associate that behavior with having fun or with good things happening.

Second, if the client perceives that all we are doing is trying to teach the dog what he or she has already learned in training class they will not see the need to comply. If we offer nothing different, what is the point of behavior modification? It is the practitioner's job to teach the client that behavior modification is about changing the way the dog thinks about interactions by rewarding the physical cues associated with the underlying physiological state. Obedience training, while sharing many similarities with behavior modification, differs in the premise, interactive reward structure, goal, and outcome. Most of the dogs that undergo behavior modification have been through some form of training and most know how to sit. For a dog to do this successfully in a class (or even a show) situation, the dog does not have to be relaxed. For behavior mod to work as well as it can the dog MUST be relaxed.

2. Relaxation is key here - the sitting and staying is merely a facilitator for the relaxation response. There is no sense to having the dog sit and stay if it is panting, salivating, its pupils are dilated, its ears are back, and it is clearly distressed. What on earth is the dog learning? It's simple - the dog is learning to be more distressed - while sitting - and also teaching his- or herself to become refractory to complex learning because of arousal of the HPA-axis (hypothalamic-pituitary-adrenal axis) (Diamond et al., 1992; Yau et al., 2002). This is why old-fashioned, out-moded, and simplistic 'sit-stay' programs so often fail: the dog sits, but is still distressed.

3. Clients will have trouble with appropriate timing of rewards and 'corrections'. 'Corrections'

should be restricted to walking away from the dog or a quick, low vocal signal that the dog is behaving undesirably. The point of the 'correction' is to interrupt the dog - not to 'get even'. If clients are doing any more than this, they are at risk for potentially - albeit accidentally - exhibiting abusive behaviors that will make the dog worse. Dogs read non-vocal or body language far better than do most humans (Cooper et al., 2003; Hare and Tomasello, 1998; Hare et al., 1998, 2002; Topal et al., 1997). It is easy for them to 'subvert' the exercise and shape the behavior of the client. Problem dogs have been doing this already, and such behaviors are NOT malicious. They ARE, however, behaviors that logically are exhibited by a confused, uncertain animal in an attempt to gain information about what can be expected - and what their response should be - within that context. Because clients so often attribute uncharitable 'motivations' to their pets someone from the outside of the relationship needs to be able to comment on timing problems and to instruct the clients when to change their posture, their tone, or their quickness of praise or reward. Most clients are quite good at learning to do this, but they need help. After the initial demonstration they may even need to be able to show you what they are doing to see if it is correct, or if you can make recommendations. This can be done in a quick 10-15 appointment (and support staff can be responsible for this), or the client can send a video, and an appointment - in person or by telephone - can be set for a critique. If the clients are not seeing an improvement, or are having an actual problem either:

- a) they are pushing the dog too hard, too fast (very common in today's hi-tech, faster-is-better world),
- b) they are giving confusing signals, or
- c) their timing is wrong.

This is hard work -- it is not magic. The practitioner will need to help along the way.

3. The practitioner and, or the staff must work WITH the client. In the case of a very fearful or very aggressive dog the practitioner may not be able to demonstrate the exercises or fit a halter during the first visit. In such cases, after fully cautioning the client about possible risks, the practitioner can ask if the client feels comfortable attempting the first round of the behavior modification protocols while the practitioner talks them through it. For reasons of liability it is important to explain that this is not the desired technique; however, if the client cannot eventually work with the dog, or if the client is perpetually afraid of the dog, the situation will be hopeless.

If the practitioner is able to work with the dog,

they should do so both to teach the dog the appropriate behaviors and to demonstrate to the clients what is desired. Again, making a video that can be played back and critiqued after the session can help. When the dog works well with the practitioner, it is the client's turn. It is not sufficient to demonstrate the behavior modification without then giving the client the chance for emulation. It is of no use if the dog is perfect for the practitioner, but a horror for the client. -- the practitioner does not have to go home and live with the dog. The clients must be able to accomplish the suggested modification, hence it is inappropriate to just send them home with sheets of paper.

If the client's dog cannot or will not work with the practitioner, the practitioner should have another dog available that can be used. This dog should be able to work with the client so that the client understands what an appropriate response is. Everyone who is serious about veterinary behavioral medicine should have a demo dog who will teach the clients and staff to hone their observational and functional skills. Alternatively, these tasks can be farmed out to someone more likely to have a good demo dog and who is uniquely equipped to teach the practical implementation of behavior modification: in the USA, an Association of Pet Dog Trainers (APDT) Certified Pet Dog Trainer (CPDT) ([www.apdt.com](http://www.apdt.com)).

4. Finally, if there is the potential for a dangerous behavior that will need to be altered or avoided, it would be optimal if the client doesn't discover this when there is no one to help them. A run-through of the program will minimize, but not ablate, this chance.

A few words about rewards: Most commonly used behavior modification programs employ praise and food treats or other rewards. The higher the quality of the treat the better the dog's response. A dog who might work for American cheese while on the property, might need dried liver when out in traffic. No one goes to hell for using food treats, but to hear people's reactions, you'd be certain this was the case.

The approach to behavior modification discussed here does not use hand signals or clickers. Clickers are unforgiving with respect to timing, and to ask a client to read a problem pet's signals, monitor them constantly, teach them to sit and relax, and incorporate the clicker system of secondary reinforcement into behavior mod, is not kind to the clients, and can further confuse the dog.

Hand signals are commonly used in obedience and can be useful for dogs and clients, but behavioral patients need every bit of help that they can get. Hand signals, here, will be a needless distraction.

Once the dogs master the programs, they will have no problems coupling the learned vocal cues to visual ones. Until then, these dogs should work in calm, quiet circumstances, without distraction, for vocal cues, and a consistent reward structure. Dogs can learn all the words for the 'commands', signals, or requests that they will need for these programs.

Most importantly, hand signals at this stage will only ask the dog to distract their attention from the behavior modification process, and, for very aggressive dogs, such signals will put the person using them at risk. Without exception, dangling body parts in front of an aggressive dog is not recommended, and will make the animal more anxious. In a worst-case scenario, hand signals can be seen by the dog as threats.

Tips for incorporating behavior mod into everyday life for ALL of your clients:

- (1) Don't single out only your problem patients for behavior mod. Wouldn't ALL of them benefit from learning to be calm as a way of seeking information from you or the client?
- (2) Cats should learn behavior mod, too.
- (3) At every single visit, teach the pet something behavioral. This is simple: ask them to sit, cock their head, and look at you for a food treat. Voila! Magic!
- (4) Practice 3.
- (5) Have the clients practice 3 with all of their dogs and cats: if any pet wants love, food, affection, water, grooming, to play fetch, to get into the car, et cetera - encourage them to sit and look at you or the clients first. In turn you - and the client - must be quiet and look at the pet. Acknowledge the signaling relationship and be clear (this works for spouses and kids, too). Then give the pet access to that which they requested.
- (6) Every member of your staff should already be practicing 3. If they are not doing so, why not?
- (7) Fit all pets with head collars and harnesses. Stock and sell these AND the know-how that goes with using them. Throw out: chain leashes, choke chains, prong collars, slip collars, et cetera.
- (8) Teach clients how to pet their dogs and cats. It's so simple it will just plumb elude them. Ask them what they want: a jazzed, reactive pet, or a calm one.....logic will carry them from here.
- (9) Reward spontaneously wonderful behaviors and teach your clients to do so by example. [Thanks for paying attention to these notes!]
- (10) Encourage gentle walking on a leash by engaging the pet in conversation....encourage your clients to avoid learning that which must be unlearned later (for them and the pet). This translates to the over-used concept of preventing - not treating - problems. While a bit overused,

the concept is valid: all management related problems can be prevented by telling the animal what you want in advance and encouraging those favored behaviors.

(11) Be reliable, signal clearly, be compassionate and humane, and let your patients make you a better person. Then pass it on to the clients.

Dogs and cats are highly cognitive animals (9,10). If you realize this and incorporate behavior modification designed to take advantage of their cognitive skills at each and every routine appointment, you may have no real behavior cases in your practice.

## References

- Bateson P. How do sensitive periods arise and what are they for? *Anim Behav* 1979, 17:470-486.
- Carter AP, Chen C, Schwartz PM, Segal RA. Brain-derived neurotrophic factor modulates cerebellar plasticity and synaptic ultra-structure. *J Neurosci* 2002; 22: 1316-1327.
- Cooper JJ, Ashton C, Bishop S, et al. Clever hounds: social cognition in the domestic dog (*Canis familiaris*). *Appl Anim Behav Sci* 2003; 81: 229-244.
- Daniel H, Levenes C, Crépel F. Cellular mechanisms of cerebellar LTD. *TRENDS Neurosci* 1998; 21: 401-407.
- Davis M. Neurobiology of fear responses: the role of the amygdala. *J Neuropsychiatry Clin* 1997; 9: 382-402.
- Diamond DM, Bennett MC, Fleshner M, Rose GM. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus* 1992; 2: 421-430.
- Duman RS. Novel therapeutic approaches beyond the serotonin receptor. *Biol Psychiatry* 1998; 44: 324-335.
- Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. *Arch Gen Psychiatry* 1997; 54: 597-606.
- Hare B, Tomasello M. Domestic dogs (*Canis familiaris*) use human and conspecific social cues to locate hidden food. *J Comp Psychol* 1999; 113: 173-177.
- Hare B, Brown M, Williamson C, Tomasello M. The domestication of social cognition in dogs. *Science* 2002; 298: 1634-1636.
- Hare B, Call J, Tomasello M. Communication of food location between human and dog (*Canis familiaris*). *Evol Commun* 1998; 2: 137-159.
- Hart BL. Environmental and hormonal influences



- on urine marking behavior in the adult male dog. *Behav Biol* 1974, 11: 167-176.
- Hopkins S, Schubert T, Hart B. Castration of adult male dogs: effects on roaming, aggression, urine marking, and mounting. *JAVMA* 1976, 168: 1108-1110.
- LeDoux JE et al. The lateral amygdaloid nucleus: sensory interface of the amygdala in fear conditioning. *J Neurosci* 1990; 10: 1062-1069.
- O'Farrell V, Peachey E. Behavioral effects of ovariectomy on bitches. *J Sm Anim Pract* 1990; 31: 595-598.
- Overall KL. Sex and aggression. *Canine Practice*. 1995; 20(3): 16-18.
- Overall KL. Clinical behavioral medicine for small animals. Mosby, St. Louis, 1997.
- Overall KL. Allow behavioral drugs ample time to take effect. *Vet Med* 1999; 94: 858-859.
- Overall KL. Behavior modifying drugs: Neurochemistry and molecular biology. *Proceedings of the 18th ACVIM Forum* 2000; 18: 68-71.
- Overall KL. Pharmacological treatment in behavioral medicine: The importance of neurochemistry, molecular biology, and mechanistic hypotheses. *The Veterinary Journal* 2001; 62: 9-23.
- Overall KL. "How dogs learn", PABA meeting notes, April 2003, Guelph, Ontario.
- Pfaffenberger CJ, Scott JP. The relationship between delayed socialization and trainability in guide dogs. *J Genet Psychol* 1959, 95: 145-155.
- Salter MW. Src, N-methyl-D-aspartate (NMDA) receptors, and synaptic plasticity. *Biochem Pharm* 1998; 56: 789-798.
- Schafe GE, Nader K, Blair HT, LeDoux JE. Memory consolidation of Pavlovian fear conditioning: a cellular and molecular perspective. *TRENDS Neurosci* 2001; 24: 540-546.
- Scott JP, Fuller JL. 1965. *Genetics and the Social Behavior of the Dog*. University of Chicago Press. Chicago, IL.
- Scott JP, Marston MV. Critical periods affecting the development of normal and maladaptive social behavior in puppies. *J Genet Psychol* 1950, 77: 25-60.
- Topal J, Miklosi A, Csanyi V. Dog-human relationship affects problem solving behavior in dogs. *Anthrozoos* 1997; 10: 14-224.
- Trotti D, Danboldt NC, Volterra A. Glutamate transporters are oxidant-vulnerable: a molecular link between oxidative and excitotoxic neurodegeneration. *Trends Pharm Sci* 1998; 19: 328-334.
- Voith VL. Teaching sit-stay. *Mod Vet Pract* April 1982: 317-320.
- Wittenberg GM, Tsien JZ. An emerging molecular and cellular framework for memory processing by the hippocampus. *TRENDS Neurosci* 2002; 25: 501-505.
- Yau JLW, Noble J, Hibbert C, Rowe WB, Meaney MJ, Morris RGM, Seckl JR. Chronic treatment with the antidepressant amitriptyline prevents impairments in water maze learning in aging rats. *J Neurosci* 2002; 22: 1436-1442.