Université de Montréal

PHYSIOLOGICAL AND BEHAVIOURAL EFFECTS OF DEXTROAMPHETAMINE ON BEAGLE DOGS : A PLACEBO CONTROLLED STUDY

par
Enid K. Stiles

Département de sciences cliniques
Faculté de médecine vétérinaire

Mémoire présenté à la Faculté de médecine vétérinaire
en vue de l'obtention du grade de
maître ès sciences (M.Sc.)
en sciences vétérinaires
option sciences cliniques

Juillet 2009

Université de Montréal
Faculté de médecine vétérinaire

Ce mémoire intitulé

PHYSIOLOGICAL AND BEHAVIOURAL EFFECTS OF DEXTROAMPHETAMINE ON BEAGLE DOGS : A PLACEBO CONTROLLED STUDY

présenté par
Enid K. Stiles, B.Sc., D.V.M.

a été évalué par un jury composé des personnes suivantes

Alain Villeneuve, président-rapporteur

Diane Frank, directrice de recherche

Sophie Cuvelliez, membre du jury

Résumé

Plusieurs articles scientifiques et manuels de référence en médecine comportementale distinguent l'hyperactivité ou hyperkinésie de l'activité excessive en évaluant la réponse physiologique et comportementale des chiens suite à l'administration per os de 0.2 à 1.0 mg/kg de dextroamphétamine. Selon ces références, le chien atteint d'un syndrome hyperactif ou hyperkinésie, répondra de façon paradoxale à cette médication par une diminution de l'activité motrice accompagnée d'une réduction minimale de 15% de la fréquence respiratoire et de la fréquence cardiaque. L'objectif de la présente étude était de mesurer la variation de la température corporelle, de la fréquence cardiaque, de l'activité motrice et de différents comportements spécifiques chez un groupe de Beagles ayant reçu de la dextroamphétamine. La fiabilité d'un accéléromètre comme mesure objective d'activité motrice a aussi été évaluée.

Dans le cadre de cette étude croisée contrôlée par placebo, douze Beagles de la colonie de recherche âgés entre 13 et 20 mois ont reçu une dose orale de 0.2 mg/kg de dextroamphétamine. Le moniteur cardiaque Polar® et un accéléromètre Actical® ont été utilisés pour enregistrer la fréquence cardiaque et l'activité motrice avant et après l'administration de la médication. La durée de chacun des comportements spécifiques a été compilée à l'aide du logiciel Noldus® et la température corporelle a été prise par thermomètre rectal. Le modèle équilibré de mesures répétées indique que les sujets ayant reçu la dextroamphétamine montrent une réduction significative ($p = 0.044$) de leur fréquence cardiaque comparativement aux chiens ayant reçu le placebo. Aucune variation significative n'a été observée concernant la température corporelle, l'activité motrice, et les autres comportements (léchage des babines, halètements, et bâillements) suite à l'administration de la dextroamphétamine. Une corrélation significative, linéaire et positive ($p < 0,0001$) entre les périodes de mouvements observées (vidéo) et les mesures d'activité enregistrées par l'accéléromètre a été observée. Les résultats de cette étude indiquent que les Beagles peuvent afficher des effets paradoxaux dans les 90 minutes suivant l'administration per os de dextroamphétamine à raison de 0.2 mg/kg.

Mots-clés : hyperkinésie, hyperactivité, dextroamphétamine, accéléromètre, activité, Beagle, canin, comportement

Abstract

Several veterinary behaviour texts/handbooks used in practice, distinguish hyperactivity or hyperkinesis from over-activity by using the physiological and behavioural responses of dogs given amphetamines. It is presumed that true hyperactive or hyperkinetic dogs given 0.2 - 1.0 mg/kg dextroamphetamine orally will paradoxically calm down, and have at least a 15% reduction in heart and respiratory rates. The purpose of the study was to measure the effects of an oral dose of 0.2 mg/kg dextroamphetamine on heart rate, body temperature, motor activity, and discrete behaviour sequences in Beagle dogs. Reliability of a collar mounted accelerometer, Actical® as an objective measure of motor activity was also investigated.

The study design was a placebo controlled cross-over study. Twelve research colony Beagle dogs (13 - 20 months old) received an oral dose of 0.2 mg/kg dextroamphetamine as treatment. Baseline and post-treatment values for body temperature, heart rate, motor activity, and general behavioural changes, were obtained using rectal temperature, video recordings and Noldus® software, Polar® monitor (heart rate), and a collar mounted Actical®. A repeated measures model indicates that dogs receiving an oral dose of 0.2 mg/kg dextroamphetamine had a significantly ($p = 0.044$) reduced heart rate compared to placebo. There was no effect of treatment on the dogs' body temperature, motor activity, or other behaviours such as "lip-licking", "panting" and "yawning". There is a significant linear and positive relationship between the gross motor activity as measured by observational video and the Actical® counts ($p < 0.0001$). Results from this study indicate that Beagle dogs may display some paradoxical effects in the 90 minutes following an oral dose of 0.2 mg/kg dextroamphetamine.

Keywords : hyperkinesis, hyperactivity, dextroamphetamine, accelerometer, activity, Beagle, canine, behaviour

Table of Contents

List of Tables

Table I

List of Figures

List of Abbreviations

ACVB	American College of Veterinary Behaviorists
ADHD	Attention-Deficit Hyperactive Disorder
BPM	Beats-per-minute
CSF	Cerebral spinal fluid
DRD4	Dopamine D4 receptor gene
DSM	Diagnostic and Statistical Manual of Mental Disorders
G	Average acceleration produced by gravity at the Earth's surface (sea level)
GABA	Gamma-aminobutyric acid
HS	Canine Hyperactivity or Hyperkinesis Syndrome
HS-HA	Canine Hypersensitivity – Hyperactivity Syndrome
MAO	Monoamine oxidase
SEM	Standard error of the mean
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
VNTR	Variable number of tandem repeats

5-HT	Serotonin

This thesis is dedicated to my husband and children, our dogs and cat, and in memory of dearest Friday and Deli-Cat.

Thanks and Acknowledgements

I would like to begin by acknowledging and thanking my supervisor, Dr Diane Frank. Without her devotion to research and faith in me, this thesis would not have been possible. Her open spirit, humane approach to veterinary behaviour medicine and skill, has been a true inspiration to me and has given me the confidence and courage to continue to work toward my board eligibility with the ACVB.

Special thanks also to Dr Clara Palestrini for her long hours collecting the data and her love for these special research dogs. Thanks to Dr Guy Beauchamp for his greatly appreciated expertise in statistical analysis and study design.

Sincères remerciements aux Drs Alain Villeneuve et Sophie Cuvelliez d'avoir accepté de présider et de participer au jury d'évaluation de ce mémoire malgré leur agenda bien rempli. J'en suis flattée.

I owe an enormous thank you to the 12 research Beagles who un-knowingly gave their time for the advancement of science.

I would like thank my parents for their support emotionally. They have always been confident in my abilities and continue to have confidence in me as I grow. I would not be the person I am today without their love, confidence and support. My father's writing and editing skills were much needed during this process and I cannot thank him enough. I will

always look up to my mother, who also did a masters thesis while I was a teenager, and I am happy to follow in her footsteps. It's never too late to follow your dream!

Finally, and most of all, I would like to thank my husband and children. When I began this masters program I was pregnant with my first child, Sacha. Taking the time to be with them in the first years of their lives, although slowing down the process of finishing my masters, was an experience and joy I will never forget. Without them, I would not have been able to complete this program and thesis. The hours spent working and time spent away from them, will not be forgotten by myself especially. The unquestioned support from my husband will stay with me forever. Thank you from the bottom of my heart Yannick, you are my inspiration, my love, my everything.

Introduction

Behaviour problems and unwanted behaviours are common reasons for relinquishment of dogs to animal shelters in North America and many of these dogs end in euthanasia (Patronek et al. 1995; Patronek et al. 1996). The human-animal bond, although very strong and evolving considerably, is not always strong enough to overcome significant canine behaviour problems. Owners with dogs suffering from behaviour problems will often go to their friends, trainers, and sometimes as a last resort, their veterinarians for assistance and advice. Unfortunately the advice given on behaviour problems by trainers and the public often relies on anecdotal or media based information instead of science-based evidence. This is turn can lead to the use of techniques and recommendations that could be harmful to the dog possibly even exacerbating or aggravating the behaviour problem. As the new specialty of veterinary behavioural medicine evolves and grows, more information is being gathered on normal and abnormal behaviours of the canine species as well as on humane and effective treatments for these problems.

As human populations move toward more urban and suburban living conditions, dogs are now expected to live often in restrictive environments, with little environmental stimulation. With little-to-no data available on what is considered “normal activity” it is even more difficult to define hyperactivity. Is it a question of breed differences (working breeds versus non-working breeds), health, environment, lack of exercise, etc.?

In human medicine, Attention-Deficit Hyperactive Disorder (ADHD) is among the most frequently diagnosed child psychiatric disorder and is estimated to affect 3 - 5% of school aged children in North America (Barkley 1996). Canine Hyperactivity or Hyperkinesis Syndrome (HS) has been recognized since the 1970's in veterinary behavioural medicine. Owners commonly describe their dogs as being "over-active" or "hyper-active", "difficult to handle", and "unable to concentrate". The current definitions of canine HS are however highly variable, inconsistent and vague. As a result, it is extremely difficult for a veterinarian to diagnose HS in a dog.

Campbell (1973) was one of the first authors to publish information on HS in the pet dog population. He notes that clinical signs may include rapid heart rate and respiration, excessive salivation, a high metabolic rate and reduced urine output. He distinguishes between hyperkinesis and hyperactivity of dogs using owner complaints as well as the use of a stimulant medication response test. The majority of veterinary behaviour reference texts and publications in North America have described the use of this stimulant (dextroamphetamine or methylphenidate) response test for the diagnosis of HS and they are all based on the initial description made in the 1970's by Corson. In general, the test includes taking baseline physiological parameters such as heart rate and respiratory rate as well as objective evaluation of the dog's activity level. The dog is then given an oral dose of dextroamphetamine (0.2 mg/kg – 1 mg/kg) or methylphenidate (0.2 mg/kg up to 1 mg/kg for an aggressive dog). If a paradoxical effect occurs then the dog will calm down, and its heart rate and respiratory rate will decrease by at least 15% from initial basal rates. This

"paradoxical" effect of CNS stimulants is observed 30 - 90 minutes post-administration of the medication (Campbell 1992; Overall 1997; Lindsay 2001; Landsberg et al. 2003; Houpt 2005).

Practitioners, trainers and the public are often commenting that overactive dogs are either genetically predisposed to high levels of energy and activity (working breeds), or their "unruly" behaviours have been inadvertently rewarded (or both). Some specialists believe that hyperactivity is over diagnosed and that in general these dogs are simply under-exercised and over-active. Owner questionnaires and temperament tests may be done by veterinarians, behaviour specialists, trainers and breeders to obtain information regarding activity of the adult dog or puppy as well as other information such as anxiety/nervousness, sociability and aggression. These subjective clinical evaluations are not well validated and most studies do not address validity issues. Objective measures of activity, such as pedometers, accelerometers, and video-tracking devices, are increasingly being used in research, however the reliability and validity of these devices is still being questioned. The expense of some of these devices will greatly influence their ability to be used in non-research center settings such as testing dogs in the public and in clinical practice.

Studies with children have shown that stimulant medications such as dextroamphetamine and methylphenidate may produce "paradoxical" effects in both normal and hyperactive children. There is a group of non-ADHD children that when given amphetamines may become less motor active and may be able to concentrate for longer periods of time. Clinical studies in combination with clinical interpretations in the field,

have led investigators and clinicians to question the abundant use of stimulants in the treatment of children with ADHD as there is likely a subgroup of children who are not truly ADHD and yet still respond paradoxically to stimulants (Zahn et al. 1980). This may be leading to the misuse and over-prescription of MPH in some cases of children who are clinically not ADHD.

In contrast to human doctors, it is rare for veterinarians, including veterinary behaviour specialists, to prescribe stimulants for the treatment of dogs suspected of suffering from HS. Are we as veterinarians' under-diagnosing, over-diagnosing or misdiagnosing this syndrome in dogs? Is this due to poor diagnostic criteria and evidence? Or is it due to the common misconception that dogs, like human children, do not have true ADHD but rather that they are simply not getting enough exercise and stimulation?

The primary objective of the present study is to measure the effects of an oral dose of dextroamphetamine on Beagles using a clinical diagnostic HS testing regimen. There are no clinical trials using the diagnostic regimen outlined in the veterinary behaviour texts and publications. What are the effects of this response test on Beagles and do some of these dogs just like children, respond paradoxically to amphetamines even when clinically not hyperactive or hyperkinetic?

In the present study, the initial experimental protocol used two different doses: 0.2 mg/kg as well as 1.3 mg/kg of dextroamphetamine. The first dog to receive the higher dose of 1.3 mg/kg displayed stereotypic behaviours 3.5 hours after receiving the oral dose as

well as an increase in body temperature to 40°C (personal communication, Dr Diane Frank). For reasons of animal welfare, the higher dose regimen was discontinued and the lower 0.2 mg/kg dose was maintained for the purpose of this study.

A secondary objective of the study was to investigate the reliability of an activity measuring device: the accelerometer (Actical®). The objective evaluation of motor activity in dogs is an area of veterinary medical research that is rapidly expanding, and tools such as pedometers, motion sensitive-video tracking and accelerometers may allow for more reliable and objective methods of monitoring. Accelerometers have not been used often in the study of motor activity in dogs and so we hope that the information collected using this device will significantly assist the development of future motor activity studies on dogs in at-home contexts.

Chapter I - Literature Review

I.1 Canine Hyperactivity or Hyperkinesis Syndrome (HS)

I.1.1 Current Definition of Canine Hyperactivity or Hyperkinesis Syndrome

The current definitions of canine Hyperactivity or Hyperkinesis syndrome (HS) are highly variable and there is very little recent literature on the subject. In 1973, W. Campbell was one of the first to publish information on hyperkinesis in the pet dog population. He describes signs associated with this syndrome as those that "are usually displayed when the dog is distressed by close confinement and/or social isolation". Campbell notes that clinical signs may include rapid heart rate and respiration, excessive salivation, a high metabolic rate and reduced urine output. He distinguishes between hyperkinesis and hyperactivity of dogs using owner complaints. Campbell claims that owners with hyperkinetic dogs will have complaints such as: "the dog cannot sit still, even for a minute; it never becomes accustomed to everyday situations; it cannot learn anything; it salivates constantly and always seems excited or nervous".

Lindsay (2001) recommends that dogs that are excessively active and "present with signs of impulse-control problems and other relevant symptoms such as attention deficits, inability to calm down, and persistent reactivity to restraint and confinement, aggressiveness and impaired learning ability and insensitivity to punishment" be evaluated for HS.

At this time, there remains a great deal of debate on the true definition of canine Hyperactivity or Hyperkinesis Syndrome (HS). Certain general textbooks/handbooks of veterinary behaviour medicine used frequently in North America (Campbell 1992; Overall 1997; Landsberg et al. 2003) claim that hyperactivity or over activity are not the same as true hyperkinesis. These handbooks/textbooks postulate that this hyperactivity (and/or over activity) can be differentiated from hyperkinesis based on the response of the patient to a test using stimulant medications. Landsberg et al. (2003) discusses that overactive dogs are either genetically predisposed to high levels of energy and activity (working breeds), or their "unruly" behaviours have been inadvertently rewarded (or both). It is also described that true Hyperkinesis or Attention Deficit Syndromes with Hyperactivity in dogs are those which exhibit paradoxical responses to stimulant medication tests.

Other definitions of these types of syndromes are described in some European veterinary behaviour manuals and transcripts. Dr Patrick Pageat has described a Syndrome called Hypersensitivity – Hyperactivity syndrome (HS-HA). HS-HA has been described as a syndrome that occurs when dog's motor activity appears to be overdeveloped (Landsberg

et al. 2003; Pageat, 1998). Some criteria noted by Pageat include absence of bite inhibition in a puppy older than 2 months of age, hypervigilance, and in some cases a reduction and alteration of the normal sleep patterns of the dog.

I.1.2 Attention Deficit and Hyperactivity in Children

It is clear from the above discussion, that canine HS-HA as well as HS do not have one compelling clinical sign associated with definitive diagnosis. In human literature definitions of these disorders have changed significantly over the past 30 years. Hyperactivity was initially considered the principle feature of a vaguely defined precursor to Attention-Deficit Hyperactive Disorder (ADHD), known as hyperkinetic reaction disorder of childhood (American Psychiatric Association 1968). As appears to be the case with the canine definitions and diagnostic criteria, the human condition has been redefined multiple times. Currently, in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV), ADHD is conceptualized as a 2-dimensional disorder, composed of symptoms of hyperactivity, impulsivity and inattention (American Psychiatric Association 1994). Debate on the most recent definitions of ADHD in humans continues in the psychiatric field of medicine.

ADHD is among the most frequently diagnosed child psychiatric disorders and is estimated to affect 3 - 5% of school aged children in North America (Barkley 1996). Treatment of ADHD involves support and education of parents, appropriate school

placement and pharmacotherapy. Hyperactivity, a central feature of ADHD, is often defined in human medicine as excessive or developmentally inappropriate levels of motor activity. Restlessness, fidgetiness, squirming in one's seat and often the appearance of being always "on the go" or as if "driven by a motor" are observed (American Psychiatric Association 1994). The use of stimulants for treatment is commonplace in human medicine, with the most frequently used drug being methylphenidate (short and long acting). A double-blind cross-over study done in 1980 by Zahn et al. discovered that dextroamphetamine affected both normal and hyperactive boys in a similar way. Both groups of children showed on average a reduced motor activity and impulsivity, improved attention and reduced heart rate prior to a reaction time test. This study in combination with clinical interpretations in the field, have lead investigators and clinicians to question the abundant use of stimulants in the treatment of children with ADHD as there is likely a subgroup of children that are not truly ADHD and respond paradoxically to stimulants. This may be leading to the misuse and over-prescription of methylphenidate in some cases of children who are behaviourally not hyperactive.

I.1.3 Factors Influencing Canine Hyperactivity or Hyperkinesis Syndrome (HS)

I.1.3.1 Normal Canine Activity and Testing Methods in Both Humans and Dogs

Use of the word “over-active” or “hyper-active” is common amongst veterinarians and the general public. Owner questionnaires and temperament tests may be done by veterinarians, behaviour specialists, trainers and breeders to obtain information regarding activity of the adult dog or puppy as well as other information such as anxiety/nervousness, sociability and aggression (Jones & Gosling 2005). Categories and labels such as “Activity” (Goddard & Beilharz 1984), “Locomotor activity” (Hennessy et al. 2001) and “Excitability and Trainability” (Hsu & Serpell 2003) are used in questionnaires and temperament tests. These subjective clinical evaluations are not well validated and most studies do not address validity issues. The psychometric properties of owner derived evaluations or assessments are often not established. Recently a thirteen item rating scale questionnaire was developed for dog owners to measure attention deficit and activity-impulsivity in their dogs (Vas et al. 2007) and its validity and reliability were measured. This questionnaire was primarily developed as a “tool for describing the typical responses of pet dogs to common stimuli in their natural environment”. Although the study indicates that this questionnaire is both valid and reliable, it does not however test for different people scoring the questionnaire other than the owners. As in human studies (Mitsis et al. 2000), there may be poor concordance between different people scoring and this should be investigated further.

A canine study evaluating the relationship among fearfulness, activity and exploration of guide dogs at varying ages, identified that as dogs get older their activity in the home, as per the dog trainer, was reduced. However, in other contexts such as on a

walk, there is only a very small reduction in this type of activity with age (Goddard & Beilharz 1984). Activity level may significantly drop as the dog ages and puppy activity may be a weak indicator of adult activity (Goddard & Beilharz 1984; Serpell & Hsu 2001).

Aged dogs in a controlled indoor housing setting were found to display fewer hours of activity and more rest periods than younger dogs (Siwak et al. 2003). Dogs with age-related cognitive impairment display more activity than normal aged dogs especially in the afternoon which parallels the results seen in human medicine with patients suffering from Alzheimer's disease. The normal sleep-wake cycle in dogs and their activity rhythms also appears to be affected by housing type and light-dark transitions (Siwak et al. 2003).

In the current version of the DSM-IV, there are over 29 disorders that require the assessment of altered activity level in people including anorexia nervosa, conduct disorders and depression (American Psychiatric Association 1994). To date there is no clear-cut objective data on how to define the levels or pattern of normal and hyperactive behaviour. Instead, there is wide use of questionnaires to assess attention skills, impulsivity and motor activity, as well as many other traits seen in children and in adults. The Conners Teacher Rating Scale (CTRS), a validated primary rating scale which in subsection IV scores overall activity of children (Conners 1969; Conners 1990) is commonly used in North America (Annex I). Other validated human ADHD questionnaires are used based on the DSM-IV criteria such as DuPauls ADHD Rating Scale. Current human diagnostic tools will include these rating scales as well as other psychometric evaluations and in some cases the use of solid-state actigraphs, and pedometers to measure the activity level of the person

(Tryon & Pinto 1994). Studies have shown that the use of actigraphs provides a valid and reliable measure of activity as well as an objective and independent standard against which to test the validity of diagnostic classifications from interviews and questionnaires (Dane et al. 2000).

I.1.3.2 Objective Measures of Activity

In a practical sense, it can be quite difficult to study behaviour of dogs in their natural environment. It may be seen as intrusive to the owner, and may be very time-consuming/laborious. Wilson & Sundgren's (1998) arena test which measures activities based on how many times a puppy or dog crosses a set of grid-lines in an empty arena, is an example of one method of measuring motor activity of the dog (Wilson & Sundgren 1998). A grid line technique was also used to measure locomotor activity in a study designed to predict problem behaviour after adoption (Hennessy et al. 2001). Pedometers and owner-reported activity were correlated at (r = 0.305) in a study by C.B. Chan et al. (2005). It was however found that pedometer accuracy differs with both size of the dog and the dogs gait (Chan et al. 2005).

Motion tracking devices and behavioural computer software that allow for the measurement of duration and frequency of chosen behaviours are becoming more common in veterinary studies. Observations by investigators can be somewhat subjective, particularly when it involves the interpretation of a particular behaviour. The presence of an

investigator (in-person/gross observation) may affect the normal behaviour of the animal being observed. The use of videotape recordings allows for continuous recording of behaviours, although this is more difficult when light is reduced (such as night-time). Use of infra-red lighting to improve video-evaluation has been helpful in these circumstances (Tontodonati et al. 2007). Telemetry devices paired with computer tracking systems as well as computer-linked video cameras have also allowed for objective method of measuring activity (Hansen et al. 2007; Tontodonati et al. 2007). Hansen et al. (2007) used a computer movement tracking system to evaluate baseline activity in dogs in an at-home setting. The purpose of the study was to determine the correlation between activity as measured by an accelerometer and videographic measures of movement and mobility in dogs (Hansen et al. 2007). The video movement tracking systems will only measure movement with a velocity and requires that the animal's position change over time and does not account for activity that occur when the position does not change, such as grooming, shaking head, eating, etc.

I.1.3.3. Accelerometers

Activity monitoring systems have been used in human activity studies and have been shown to reliably measure motor activity in humans. Accelerometers are devices which monitor the occurrence and intensity of motion and allow for continuous, objective, and quantitative evaluation of physical activities. These devices integrate the amplitude and frequency of motion by producing an electrical current that varies in magnitude. These

accelerometers are sensitive to movement in all directions. The piezoelectric sensor is the functional device of the accelerometer and will generate a voltage change when the device is subjected to a change in velocity. This acceleration is filtered and passed into a converter system which then creates a digital value.

The accelerometers themselves will vary somewhat between companies, as to unit size and minimal force measured (0.01G – 4.0G). Some accelerometers can be set for the minimal threshold force needed to cause an "activity count" as well as the memory of the meter (from seconds to minutes). Yamada and Tokuriki (2000), measured spontaneous activity in Beagle dogs in a cage setting using an accelerometer and studied the effect of movements on activity counts. When the threshold of the accelerometer and the amount of acceleration volume were set at 0.10G and 251 or more, then only movements of the whole-body and change in posture (such as sitting) were recorded as activity counts. At lower thresholds, such as 0.02G, more subtle movements were recorded by the accelerometer such as head movement (Yamada & Tokuriki 2000).

The accelerometers used in veterinary research are presently small in size and light in weight. They can therefore be worn easily on various parts of the body using collars or vests, and stockings. Hansen, et al. (2007), also investigated the location and method of attachment of the accelerometer on the dog. The ventral neck collar mounted accelerometer had the highest correlation coefficient (0.88) between activity counts, distance traveled and time spent mobile. Other areas, such as the humerus, had lower correlation, suggesting that the collar mounted device is likely the best location and is also the most convenient

location on the dog. A recent study by Lascelles, et al. (2007) investigated the correlation of a neck mounted accelerometer and client-specific measures of pain in cats suffering from osteoarthritis in the home setting. A client-specific outcome questionnaire was used to determine if the owner had noticed altered activity in their cat (simple yes/no questions). This study showed that accelerometers may generate objective data which could be used to validate subjective assessments of pain such as outcome questionnaires. The accelerometer may also be a useful tool to measure activity of cats in an at-home setting and may be used to detect behaviour changes associated with pain in cats (Lascelles et al. 2008).

The use of objective measurements gives the investigator the added advantage of further defining the hyperactivity in terms of quantity and pattern rather than simply categorically. The accelerometer however does not provide any information regarding the level of co-ordination of movements, the purposefulness, appropriateness or the goal directedness of the activity it is recording, which in human studies may be important information. Even given its shortcomings objective tools such as the accelerometer can be used as an adjunct to conventional diagnostic tools that rely strictly on the subjective evaluation of the patient.

I.1.4 Potential Underlying Mechanisms of Canine Hyperactivity or Hyperkinesis Syndrome

Several amino acids are found in high concentration in the brain, and some have been identified as neurotransmitters. Neurotransmitters in the brain include monoamines: norepinephrine, dopamine and serotonin (5-HT), and peptides (such as vasopressin). A dog's nervous system activity is a result of interplay between excitatory and inhibitory neurotransmitters. Glutamic acid (glutamate) is the major amino acid neurotransmitter for fast excitatory synaptic transmission. Gamma-amino-butyric acid (GABA) is the major amino acid neurotransmitter for the fast inhibitory synaptic transmission. Some other neurotransmitters, such as dopamine, depend on the receptor at the synapse to determine whether the transmitter is excitatory or inhibitory.

It has been hypothesized that dogs suffering from HS may suffer from a lack of neurotransmitters in the inhibitory centers of the brain (Campbell 1992; Lindsay 2001), specifically dopamine. In humans, depressed dopamine activity was found in adults with ADHD (Volkow et al. 2007). Dopamine and epinephrine are primarily neurotransmitters that produce arousal. Dopamine has many functions in the brain including cognition, sleep, attention, motor activity and motivation. Cortical inhibitory processes will modulate excitatory neuro-activity, keeping motor activity regulated and controlled. These processes can be thought of as a "control switch" made of a succession of 3 neurons: a dopaminergic neuron coming from the striatum (subcortical part of the cerebrum), and two GABAnergic neurons situated in the nucleus accumbens and the ventral pallidum of the brain. These neurons then connect with motor-neurons (Lindsay 2001; Dehasse 1999). All these neurons are firing spontaneously and inhibit the next neuron, creating an "electrical switch". As is

postulated with people suffering from ADHD, dogs affected by HS may have a lack of inhibitory action in the brain and so their "control switch" is often in the "on-position".

Animal studies using knockout mice that lacked serotonin (5-HT 1B) receptor showed a marked increase in motor activity (Brunner et al. 1999). A selective 5-HT reuptake inhibitor, fluoxetine, has been shown to attenuate hyperactivity in knock-out mice that lack the gene responsible for encoding the dopamine transporter (Gainetdinov et al. 1999). These studies have led researchers to continue investigating the role of serotonin transporters in ADHD as well as the effects of psychostimulants on serotonin transporters.

Genetic polymorphism within the dopamine D4 receptor (DRD4) gene has been linked to ADHD (Faraone et al. 2005). Given these results, it is thought in humans that ADHD is highly heritable (Shaw et al. 2007). In canine studies, the D4 receptor is also thought to be involved in HS, and has been found to be responsible for "novelty seeking" behaviours with the long allele having the higher tendency for novelty seeking (Niimi et al. 1999).

I.1.5 Diagnostic Methods for Canine Hyperactivity or Hyperkinesis Syndrome

Corson and Corson (1976) describe a naturally occurring Telomian-Beagle hybrid dog model whose behaviour closely resembled that of children suffering from hyperkinesis

(as defined at that time). These Telomian-Beagle hybrid dogs had been shown to exhibit hyperactivity, impulsiveness and impaired learning and were unable to be trained in a Pavlovian stand either with positive or negative feedback. When Corson and Corson (1976) treated these hybrid dogs with dextroamphetamine, they found variability in response to treatment. Some of the hybrid dogs began to respond to Pavlovian conditioning while others did not. These responders also displayed some physiological changes as well as behaviour changes with the stimulant medication. The "hyperkinetic" amphetamine responder dogs became "normalized" and trainable with dextroamphetamine doses of 0.2 - 1.0 mg/kg *per os* (Arnold et al. 1973; Corson & Corson 1976; Corson et al. 1980). Approximately 60% of dogs which were classified as being hyperkinetic responded paradoxically to stimulants. These studies allowed for the use of dogs as a model for hyperkinesis in children as well as pursue further investigation of the disorder in the canine species.

All present literature refers back to the Corson et al. studies and it was on the basis of these studies that Campbell in 1973, developed a preliminary clinical test for hyperkinesis which has since repeatedly been recommended in many behaviour texts. This test has not been validated. The procedure is as follows:

1. "Without the client present the dog's pulse and respiration are recorded in the smallest examination room available.

2. Salivations (heavy, light, none) are noted and the client is questioned about the dogs urination pattern for evidence of antidiuresis.

3. Muscle tone and general activity are noted.

4. Oral dextroamphetamine is administered at a dose of 0.2 mg/kg orally and then the dog is taken to a holding area.

5. After 75 minutes minimum, and using a different small examination room, the pulse, respiratory, salivation and muscle tone and general activity are recorded.

6. If the dog displays higher readings and increased muscle tone and activity it is presumed the amphetamine has produced normal response and the dog is not hyperkinetic. If the opposite is true, the dog is likely hyperkinetic." (Campbell 1973).

Luescher (1993) repeated the Campbell test with 6 cases and remarked that paradoxical effects were often seen as early as 30 minutes after receiving the oral dextroamphetamine. Campbell (1992) and Overall (1997), state that dogs may be diagnosed as hyperkinetic if they have a $\geq$ 15% decrease in heart rate and respiratory rate 75 - 90 minutes after receiving 0.2 - 1.0 mg/kg of methylphenidate. Houpt (2005) recommends a dose of 0.5 mg/kg of amphetamine (not specified as to which amphetamine should be used) and then repeating heart rate and respiratory measures 30 to 60 minutes after receiving the medication. Landsberg et al. (2003), also recommends the stimulant test, at a dose of 0.2 - 0.5 mg/kg of

dextroamphetamine and monitoring effect every 30 minutes for 2 hours. Houpt (2005) and Landsberg et al. (2003) do not define the amount of reduction in respiratory rate, activity, or heart rate necessary to diagnose hyperactivity.

Other sources use response of a trial treatment of amphetamines as a diagnostic method. Voith (1980) recommends simply doing a trial with the stimulant medication and gradually increasing the dose by small increments until effective dose is reached. Landsberg et al. (2003) also recommends the use of an oral low-dose of methylphenidate at 0.5 mg/kg twice daily with increasing increments of 0.25 mg/kg to effect up to a maximum of 2 mg/kg twice daily.

I.1.6 Therapeutic Management of Canine Hyperactivity or Hyperkinesis Syndrome

Management of HS has generally encompassed two areas of therapy: behaviour and environmental modification as well as pharmacological treatment. References will describe either simply using behaviour modification or using a combination of both pharmaceutical intervention and behaviour modification. Some references will determine which therapy to use depending on the response of the patient to a stimulant trial (see I.1.5). In all references, behaviour modification is always an integral part of treatment, with or without pharmacological intervention.

I.1.6.1 Behaviour Modification and Environmental Modification

Various forms of behaviour modification have been outlined as sole or adjunct therapy for dogs suffering from HS. Some sources, such as Overall (1997), claim that true hyperkinesis is rare and in such cases, behaviour modification is generally the sole treatment option. Landsberg et al. (2003) discuss canine hyperactivity concomitantly with unruliness and outline the need for increased exercise and play when treating these problems.

Common veterinary behaviour references such as Voith (1980), Houpt (2005), Landsberg et al. (2003), and Overall (1997), discuss behaviour modification for HS cases with congruency. Voith (1980) summarizes a group of behaviour modification techniques to be employed with "playful aggressive behaviour or hyperactivity". She recommends the single or combined use of methods such as extinction (ignoring the activity until it extinguishes itself), re-direction (re-directing the dog from exuberant inappropriate behaviours to a more acceptable behaviour), counter-conditioning (teach the dog a response that is incompatible with the undesirable behaviour) and punishment. Houpt (2005) outlines that if the dog is fine in the absence of the owner then increased exercise, a canine companion, and training may suffice to improve the dog's behaviour. The positive reinforcement of calm behaviours is also mentioned in many references. Landsberg et al. (2003), focus on the unintentional and inadvertent reinforcement of undesired exuberant

and attention seeking behaviours by the owners. Extinction techniques and deference programs are therefore recommended as behaviour modification techniques. There are no studies to date that investigate the efficacy of any of the above behaviour modification techniques. Pageat (1998) recommends the use of "therapy by games" and learning programs to teach dogs social inhibitions. For example, if when playing a game with the dog, it begins to engage in behaviour other than the game itself (such as jumping on the person), then Pageat recommends cessation of any interaction with the dog. In general, Pageat will recommend beginning pharmacological treatment for a minimum of 3-4 weeks before initiating behaviour modification, to ensure the dog's overall activity is bearable by the owners (Pageat 1998). The use of pharmacological treatment prior to the initiation of behaviour modification has not been validated.

I.1.6.2 Pharmacological Treatment

Most psychotropic medications used in the treatment of HS are based on the hypothesized underlying neuro-chemical mechanism of this syndrome. As will be discussed later (section II.2), dextroamphetamine and other stimulants such as methylphenidate, will affect certain neurotransmitters and either prevent their re-uptake and/or cause them to increase stimulation of post-synaptic receptors (Patrick & Markowitz 1998). Stimulant medications have been recommended by authors for the treatment of HS however the

discussion of their efficacy and long-term use is questioned by many of these same authors (Overall 1997; Lindsay 2001; Landsberg et al. 2003).

Campbell (1973), recommends using 0.2 mg/kg dextroamphetamine three times daily and to increase the dose of the medication by 50% on consecutive days until the desired response is achieved. Cases reported by Campbell (1992), report therapeutic doses ranging from 0.5 - 1 mg/kg. Luescher (1993) describes the use of dextroamphetamine for the six canine HS cases reported at doses between 0.2 - 0.5 mg/kg dextroamphetamine as trial, however he also discusses the use of tricyclic anti-depressants (TCA), and methylphenidate for dogs who do not respond paradoxically to dextroamphetamine. Landsberg et al. (2003), recommend using methylphenidate at low doses of 0.5 mg/kg twice daily and gradually increasing the dose by 0.25 mg/kg increments every 2 days until the desired response is achieved up to a maximum dose of 2 mg/kg twice daily.

The effectiveness of amphetamines (dextroamphetamine and methylphenidate) in controlling HS may be partly due to the release of 5-HT (serotonin), either directly or via action of released dopamine at 5-HT neurons. As such, SSRIs (selective serotonin reuptake inhibitors) such as fluoxetine hydrochloride and TCAs such as clomipramine hydrochloride have also been recommended for treatment in some cases (Voith 1980b; Luescher 1993; Lindsay 2001; Landsberg et al. 2003). Dehasse (1999) and Pageat (1998) claim that because a lack of dopamine may be causing overactivity at the control switch in the brain, treatment with inhibitors of monoamine oxidase (MAO), such as selegiline for HA-HS dogs may be beneficial. Selegiline prolongs the effects of dopamine in the brain by

preventing its breakdown. It is stipulated, however, that the treatment effect of selegiline with dogs suffering from HA-HS may be in part due to the fact that selegiline is partly metabolized to methamphetamine and l-amphetamine. In other cases, Pageat (1998) also recommends the use of normothymic (mood stabilizer) medications such as valproic acid and carbamazepine. It is important to note, that none of these pharmacological treatments have been validated in peer reviewed publications.

I.2 Dextroamphetamine (S)-1-phenylpropan-2-amine sulfate

Dextroamphetamine (dexamphetamine, *d*-amphetamine) is the dextrorotary stereoisomer of the amphetamine molecule which can take 2 forms: *d*-isomer and *l*-isomer (Baggot & Davis 1973).

I.2.1 Mechanism of Action

The exact mechanism of action of dextroamphetamine is unknown. Studies describe its actions as stimulating central nervous system activity, blocking reuptake and increasing release of norepinephrine (sympathomimetic) and dopamine in extra-neuronal space. Dextroamphetamine affects dopamine and serotonin levels in the nucleus, and norepinephrine in the hippocampus of the brain (http://en.wikipedia.org/wiki/

Hippocampus). Dextroamphetamine is a substrate analog at monoamine transport, and regardless of dose, it prevents the reuptake of the monoamine neurotransmitters causing them to remain in the synaptic cleft for prolonged periods (Kuczenski et al. 1995). When doses are high, dextroamphetamine will enter nerve cells and cause release of monoamines from the cytoplasmic dopamine pool. In such high concentrations, dextroamphetamine will cause the norepinephrine, dopamine, and 5-HT transporters to reverse their direction of flow. This inversion leads to a release of these transmitters from the vesicles to the cytoplasm and from the cytoplasm to the synapse causing increased stimulation of post-synaptic receptors (Patrick & Markowitz 1998). Overall, their stimulant action is produced by releasing catecholamines from adrenergic nerve terminals, inhibiting re-uptake of catecholamines into storage sites, releasing 5-HT and dopamine from pre-synaptic terminals, inhibiting MAO, and also by preventing monoamine reuptake (Diniz et al. 2003).

I.2.2 Pharmacokinetics of Dextroamphetamine

In humans the primary site of pre-systemic metabolism is likely to be the gut and/or intestinal wall. There is little information available in the literature on the site of pre-systemic metabolism in the dog as compared to the human metabolism. In the canine species, the biological half-life of dextroamphetamine was found to be 4.5 +/- 0.24 hours (Baggot & Davis 1973). Approximately 1/3 of dextroamphetamine will be excreted unchanged in urine in dogs which differs from humans where the percentage is closer to

50% (Baggot & Davis 1973). The renal clearance in dogs suggests that the extent of re-absorption increases with increased urinary pH. The other 2/3 of dextroamphetamine is broken down into various metabolites such as benzoic acid. The main metabolic pathway is dextroamphetamine → phenylacetone → benzoic acid → hippuric acid. Another pathway, mediated by enzyme CYP2D6, is dextroamphetamine → p-hydroxyamphetamine → p-hydroxynorephedrine. It does not appear that the extent of plasma protein binding significantly affects the pharmacokinetics of this drug in the dog (Baggot & Davis 1973).

Maximal plasma concentrations (Cmax) of dextroamphetamine were achieved in male dogs between 1 - 2 hours following a single oral doses of 1.5 mg/kg (Bareggi et al. 1978). The plasma concentration of dextroamphetamine remaining at 8 hours in this study following a dose of 1.5 mg/kg was approximately 20% of Cmax (Bareggi et al. 1978).

Behavioural effects of dextroamphetamine in humans are increased by larger doses, however, over the course of a given dose there is a divergence between such effects and drug concentration in the blood (Angrist et al. 1987). In particular, mental effects peak before maximal blood levels are reached, and decline as blood levels remain stable or even continue to increase.

Bareggi et al. (1979) found that behavioural responses of the Telomian-Beagle hybrid dogs depended on the amount of plasma amphetamine which in turn was linearly related to the amount in the CNS. It appears that amphetamine peaks and is eliminated from

the CSF at the same time as it is in blood plasma (Bareggi et al. 1979a). In these studies, responder dogs had higher and earlier peak levels of amphetamine than non-responder dogs (Bareggi et al. 1978; Bareggi et al. 1979a). Responder dogs were those Telomian-Beagle hybrid dogs that responded in a paradoxical manner to amphetamine (dogs able to respond with appropriate behaviour to certain training tests which they were unable to perform prior to medication). In these studies there was another group identified as the non-responder Telomian-Beagle. These non-responder dogs were unable to perform during training tests, even after receiving amphetamine.

I.2.3 Paradoxical Effect of Dextroamphetamine

Pharmaceutical paradoxical effects are those that exhibit inexplicable or contradictory effects. The clinical appearance of paradoxical effects with dextroamphetamine is the basis behind the treatment of certain psychiatric disorders with these medications. The dose of dextroamphetamine necessary for the "paradoxical" effect to be observed in HS dogs is not known. In general dextroamphetamines in the normo-active dog may cause increased stereotypic behaviours (Randrup & Munkvad 1967), CNS excitation, cardiovascular effects (tachycardia), hyperthermia, and some gastrointestinal effects (Bareggi et al. 1978; Tontodonati et al. 2007).

As discussed earlier in sections I.2.1 and I.2.2, stimulants may cause a reduction in clinical signs of HS through various neurochemical processes. Once given

dextroamphetamine, dogs that display reductions in heart rate, motor activity, respiratory rate and body temperature are labelled as displaying paradoxical effects of this medication.

I.2.4 Clinical Applications of Dextroamphetamine

Primarily, dextroamphetamine is used to treat ADHD and narcolepsy in humans. Stimulants are used to treat people and children suffering from ADHD in an attempt to decrease inattention and to increase self-control. In some countries dextroamphetamine has replaced methylphenidate as the first-choice medication for ADHD, a role in which it is considered highly effective. During the treatment of narcolepsy, patients will often experience tolerance to the therapeutic effects of stimulants (Kaplan & Sadock 1993). Dextroamphetamine and other sympathomimetics may also be used to treat depression in people that are treatment resistant or if commonly used antidepressants are contraindicated. Patients may be placed on sympathomimetics if the risk of adverse effects from TCAs or tetracyclic antidepressants and MAO inhibitors is high such as with the elderly. In some cases, dextroamphetamine will be used to differentiate human geriatric pseudo-dementia depression from true dementia. If they respond positively to the stimulant therapy then they are presumed to suffer from depression and not dementia. The long term use of stimulants to treat depression is controversial because of the potential for abuse of the drugs (Kaplan & Sadock 1993).

In behavioural veterinary medicine the most common therapeutic use of dextroamphetamine is for canine HS, narcolepsy, and aggression (if related to HS). The

doses recommended for treatment of HS have previously been discussed. In the treatment of canine narcolepsy, the dose of 5 – 10 mg dextroamphetamine three times daily has been recommended (Allen et al. 1998).

I.2.5 Contraindications and Adverse Effects

Dextroamphetamine, a CNS stimulant, is generally contraindicated in humans and animals suffering from cardiovascular disease, diabetes mellitus, anxiety, glaucoma, hypertension, concurrent MAO therapy and those suffering from hyperthyroidism (Canadian Pharmacists Association 2007; Crowell-Davis 2006). In humans, cardiovascular adverse effects such as palpitations, tachycardia, and hypertension may be seen. Effects on the CNS may include overstimulation, restlessness, dizziness, euphoria, dysphoria, and headache, exacerbation of motor or other tics, and rarely psychotic episodes. In humans it has also been shown to cause diarrhea, loss of appetite, constipation and dry-mouth (Canadian Pharmacists Association 2007). In 2006, GlaxoSmithKline Inc., manufacturer of Dexedrine® (dextroamphetamine sulfate) made revisions to the warning label of the product. The warnings describe reports of sudden death in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. As per GlaxoSmithKline (2006) “although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities,

cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug".

Amphetamines have been implicated as a potential source of thrombocytopenia in dogs (Allen et al. 1998).

It is hypothesized that patients that do not suffer from HS will exhibit increased arousal and activity with dextroamphetamine. In dogs, it appears that dextroamphetamine at doses of 1 - 2 mg/kg may induce various stereotyped behaviours, including bobbing, head turning, circling, pacing and sniffing (Wallach et al. 1971). Canine case reports of amphetamine intoxication from the Veterinary Hospital of the University of Minnesota observed hyper-excitability and agitation within 1 - 2 hours after ingestion (Stowe et al. 1976). A 90-day oral gavage canine toxicity study of *d*- and *d, l*-methylphenidate found there to be no-observed-adverse-effect at doses of methylphenidate up to 3 mg/kg. At higher doses (up to 20 mg/kg), side-effects such as reversible salivation, hyperactivity and diarrhea were seen (Teo et al. 2003). Healthy Beagle dogs displayed stereotypic behaviours peaking 2.5 hours and 6 hours post administration of amphetamine orally (2.5 mg/kg) (Bareggi et al. 1978). This study also found that normal Beagle dogs suffered from increased body temperature with peak temperatures at 1.5 hours post-administration of amphetamine suggesting that temperature changes are directly related to the presence of amphetamine in the plasma. It is postulated that the later peak of stereotypy seen in these

dogs may be a result of the amphetamine metabolite *p*-hydroxy-amphetamine (Bareggi et al. 1979b).

A recent study performed by Tontodonati et al. (2007) discovered results similar to those described above. The Beagle dogs' heart rate increased significantly at 1.5 mg/kg of dextroamphetamine, between 1 and 20 hours after treatment. At lower doses of 0.25 mg/kg and 0.75 mg/kg there was no effect on heart rate. Body temperature was found to increase significantly with the dextroamphetamine doses of 0.75 and 1.5 mg/kg (up to 1.2 and 2.5 °C, respectively), but no significant change at 0.25 mg/kg. No significant change in behaviour for most dogs receiving low dose of 0.25 mg/kg was seen, however one dog at this dose did show excitement with vocalizations and stereotyped circling between 0.5 and 2 hours after dosing. At 0.75 and 1.5 mg/kg all dogs showed excitement associated with hypersalivation and vocalization and these changes mainly occurred between 0.5 and 14 hours after dosing. It is unclear from the study results what percentage of dogs in the study actually displayed stereotypic behaviours and at which dosing regimen. It was noted however that dogs displayed individual tendencies with respect to which stereotypy they would display. Stereotypic behaviours noted included: circling, fly snapping, head bobbing, repetitive standing, lateral movements and repetitive forward and backward pacing. (Tontodonati et al. 2007).

In studies using "normal" dogs trained to pedal press for drinking water in a non-cued, single-spatial alternation task (SSA), doses of 0.15 - 0.60 mg/kg of dextroamphetamine, caused a decrease in the total number of correct responses and an increase in the

total number of incorrect responses in a dose-dependent manner (Risner & Jones 1979). This study suggests that some dogs may respond behaviourally in a dose-dependent way to low doses of dextroamphetamine.

The co-administration of sympathomimetics (such as dextroamphetamine) with TCAs, warfarin, primidone, phenobarbital, phenytoin, or phenylbutazone, will decrease the metabolism of these compounds and result in increased plasma levels of the non-sympathomimetic drug. In general it is not recommended that amphetamines be given with or within 2 weeks of administration of MAO inhibitors (Kaplan & Sadock 1993).

In the case of overdose, gastric lavage or activated charcoal is recommended. Sedatives such as chlorpromazine and acepromazine (found commonly in veterinary facilities in North America) are also recommended to reduce CNS excitation resulting from overdose of amphetamines (Canadian Pharmacists Association 2007; GlaxoSmithKline. 2006). Other sources indicate the use of diazepam at a total dose of 2.5 - 20 mg IV for dextroamphetamine overdose (Allen et al. 1998). Increasing renal excretion of the medication by acidifying the urine is controversial and not recommended at this time.

Chapter II Article

Presentation in form of an article

Physiological and Behavioral Effects of Dextroamphetamine on Beagle Dogs

E.K. Stiles [a]*, C. Palestrini [b], G. Beauchamp [a], D. Frank [a]

[a] Université de Montréal, Faculté de Médecine Vétérinaire, Centre Hospitalier Universitaire Vétérinaire, C.P. 5000, St-Hyacinthe, QC, Canada, J2S 7C6

[b] Dipartimento di Scienze Animali, Sez. di Zootecnica, Facoltà di Medicina Veterinaria, Università degli Studi di Milano, Via Celoria 10, 20133, Milano Italy

*Corresponding author: petbehavior@gmail.com

Prior publications:

1. Abstract in Proceeding of the ACVB/AVSAB Scientific Meeting July 2008
2. Abstract in Proceedings of the 6th International Veterinary Behaviour Meeting, June 2007

II.1 Abstract

Objective: The purpose of the study was to measure the effects of 0.2 mg/kg dextroamphetamine on body temperature, heart rate, motor activity, and associated behavior changes in Beagles. Reliability of a collar mounted accelerometer as an objective measure of motor activity was also investigated by comparing motor activity to that observed using video recordings.

Design: Placebo controlled cross-over study

Animals: 12 research colony Beagle dogs (13-20 months old)

Procedures: Beagle dogs served as their own control receiving both placebo and 0.2 mg/kg dextroamphetamine as treatment. Baseline and post-treatment values for body temperature, heart rate, and motor activity, were obtained using a rectal temperature, heart rate monitor, and a collar mounted accelerometer. Behavior sequences were filmed and analyzed.

Results: Repeated measures model indicates that dogs receiving 0.2 mg/kg dextroamphetamine had a significantly ($P = 0.044$) reduced heart rate compared to placebo. There was no effect of treatment on the dogs' body temperature, motor activity or other behaviors such as "lip-licking", "panting" and "yawning". There was a significant linear

and positive relationship between the gross motor activity as measured by observational video and the accelerometer counts ($P < 0.0001$).

Conclusion and Clinical Relevance: Several behavioral textbooks used in clinical practice distinguish canine hyperactivity-hyperkinesis from over-activity by physiological and behavioral response to amphetamines in a clinical setting. These authors suggest that true hyperactive-hyperkinetic dogs given oral amphetamines will paradoxically calm down, and have more than a 15% reduction in heart rate. However no data exist on the various effects of a low dose (0.2 mg/kg) of oral dextroamphetamine in dogs. The results of this study indicate that although as a group the medicated dogs showed a significantly lower heart rate than the placebo group, individual Beagle dogs showed variability in changes of heart rate. The use of the accelerometer in this study shows that it is a reliable tool for measuring motor activity in the dog.

II.2 Introduction

Canine Hyperactivity or Hyperkinesis Syndrome (HS) has been recognized since the 1970's in behavioral and veterinary medicine.[1-6] Owners commonly describe their dogs as being "over-active" or "hyper-active", "difficult to handle", and "unable to concentrate". The current definitions, however, of HS are highly variable, inconsistent and vague. In 1973 Campbell was one of the first to publish information on HS in the pet dog population.[1] He noted that clinical signs may include rapid heart rate and respiration,

excessive salivation, a high metabolic rate and reduced urine output. He distinguished between hyperkinesis and hyperactivity of dogs using owner's complaints. Campbell claimed that owners with hyperkinetic dogs would have comments such as: "the dog cannot sit still, even for a minute; it never becomes accustomed to everyday situations; it cannot learn anything; it salivates constantly and always seems excited or nervous".

Use of the words "over-active" or "hyperactive" are common among veterinarians and the general public. Owner questionnaires and temperament tests may be carried out by veterinarians, behavior specialists, trainers and breeders to obtain information regarding activity of the adult dog or puppy as well as other information such as anxiety, nervousness, sociability and aggression. Categories and labels such as "Activity"[7] and "Locomotor activity"[8] and "Excitability and Training"[9] are used in such questionnaires and temperament tests. These subjective clinical evaluations are not well validated and most studies do not address validity issues.[10] Psychometric properties of owner derived evaluations or assessments are often not established. Objective measures of activity are often difficult to make quantitatively and more research is needed to assess new techniques.

At present time, there remains a great deal of debate on the true definition of Canine HS. Certain general texts of veterinary behavioral medicine used in North America claim that hyperactivity or over activity are not the same as true hyperkinesis.[4,6,11] One author[4] asserts that overactive dogs are either genetically predisposed to high levels of energy and activity (working breeds), or their "unruly" behaviors have been inadvertently rewarded (or both). Overall[6] states that hyperactivity is over diagnosed and that in general these dogs are

simply under-exercised and over-active. Many authors[3-6,11] postulate that canine hyperactivity (and/or over activity) can be differentiated from true HS based on the response of the dog to a challenge test using stimulant medications, such as dextroamphetamine or methylphenidate. The recommended stimulant-response tests for HS vary somewhat between authors. In general, the recommended test although not validated includes taking baseline physiological parameters, such as heart and respiratory rates as well as objective evaluation of the dog's activity level. The dog is then given an oral dose of dextroamphetamine (0.2 mg/kg - 1.3 mg/kg) or methylphenidate (0.2 mg/kg - 1 mg/kg). If the dog calms down, and its heart rate and respiratory rate decrease by at least 15% from initial basal rates, this is referred to as a paradoxical effect of CNS stimulants. The criteria for this test suggest that a "paradoxical" effect would be observed 30 - 90 minutes post-administration of the medication.[6,11,12] Two authors[3,4] did not specify an amount of reduction in heart rate, respiratory rate or behaviors, except to note that they would generally be reduced if a paradoxical effect was seen. However to the authors' knowledge there is no published data on the various effects of a low dose (0.2 mg/kg) of oral dextroamphetamine in dogs. Given that the starting dose of the recommended stimulant test for HS is 0.2 mg/kg investigating the effects of this dose on dogs would be of significant interest.

The primary purpose of this study was to measure the effects in Beagles of an oral dose of 0.2 mg/kg of dextroamphetamine on body temperature, heart rate, motor activity, and associated changes in behavior. It was hypothesized based on prior studies[13,14] that the accelerometer would positively predict the activity measured by observational studies.

Therefore the reliability of a collar mounted accelerometer as an objective measure of motor activity in the dog was also investigated.

II.3. Materials and Methods

II.3.1 Subjects

A total of 12 intact Beagle dogs, 6 males and 6 females, belonging to the animal care facility of the Faculty of Veterinary Medicine, and ranging in age from 13 to 20 months were used for the study. Physical examination of all Beagles included in the study was unremarkable. The study protocol followed Canadian Council on Animal Care guidelines and was approved by the Animal Care Committee of the Faculty of Veterinary Medicine.

II.3.2 Study design

A placebo controlled cross-over study was performed (Figure 1) allowing for the collection of baseline, placebo and treatment data for all 12 dogs. A *crossover* study is one in which two or more treatments are applied sequentially to the same subject. The advantages are that each subject then acts as its own control and so fewer subjects are required. All data were collected in the same room and by the same person over a period of one month. Following a 90 minute baseline data collection, dogs received either dextroamphetamine (0.2 mg/kg) or placebo treatment. The dextroamphetamine was placed in a teaspoon of highly palatable canned food and the placebo entailed simply giving a

teaspoon of the same food without any medication. In Sequence 1 (placebo; medication), dogs 1 to 6 received one placebo treatment on Day 0 and one dextroamphetamine treatment (0.2 mg/kg) 10 to 14 days later. In Sequence 2 (medication; placebo), dogs 7 to 12 received one dextroamphetamine treatment (0.2 mg/kg) on Day 0 and received one placebo treatment, 10 to 14 days later. The minimal interval between treatments was set at 10 days based on the estimated wash-out time of dextroamphetamine in dogs and multiplying this time by 10 and then doubling that time. Using first order principles, elimination of a drug is near complete after 4 - 5 passes of the estimated half-life of the drug[15] which for dextroamphetamine in the dog was previously found to be 4.5 hours +/ 0.24.[16]

II.3.3 Data collected

II.3.3.1 Body Temperature

Baseline rectal temperatures were recorded at time 0, then at 90 minutes just prior to the administration of placebo or medication and then again at 180 minutes (90 minutes after treatment).

II.3.3.2 Heart Rate

A chest mounted heart rate monitor[a] (Figure 2) at time 0 was attached on a strap fitted around each dog's thorax in the axillary region. The monitor collected a reading of heart beats per minute every 5 seconds over the duration of the study periods. These results were downloaded to a computer after each 90 minute testing period.

II.3.3.3 Video Analysis and Behavioral Categories

Each dog was filmed for two 90 minute periods (180 minutes total) by the same person. This person did not interact with the dogs even if the dogs tried to solicit attention. Video-recorded behaviors were compiled using computer software[b] and were reviewed by one person who was blinded throughout the study. Behavioral classifications are outlined in Table 1. The category of Gross Motor Activity included mutually exclusive observations of "immobile", "locomotion", "exploration", "not-visible" and "other", measured as state events (duration). Facial behaviors included "lip-licking", "panting", "yawning", "not-panting", and "not-visible". "Yawning" and "lip-licking" were tabulated as point events (frequency) whereas "panting", "not-panting" and "not-visible" were measured as state events.

II.3.3.4 Accelerometer

All dogs were fitted with a collar that had a mounted accelerometer[c] (Figure 3). The accelerometer is a physical activity monitoring system, which integrates the amplitude and frequency by producing an electrical current that varies in magnitude. The accelerometer is omni-directional and senses any motion with a minimal force of 0.01G. It is most sensitive to movement in the direction parallel with the longest dimension of the accelerometer case. The ventral portion of the neck collar was found to be the best location for the accelerometer location.[13] Measurement period used in this study was set at every 15 seconds. Every 15 seconds the voltage generated within the accelerometer was compressed and converted into an integer and reported as an activity count. The data was then downloaded to a computer by placing the accelerometer unit into a telemetric reader after each study period.

II.3.3.5 Statistical Analysis

To evaluate the effect of treatment in this placebo controlled cross-over study, balanced repeated measures models were used for the following data: temperature, heart rate, accelerometer counts, and some observational results (percentage time spent "immobile", time spent "exploring", and frequency of "lip-licking"). The balanced repeated measures model used treatment (placebo versus medicated) as the repeated factor, the sequence of treatment (Sequence 1 and Sequence 2) as a nest factor, and baseline measures as a co-factor (to control for possible differences among individuals in baseline values). For less frequent observations, the Cochran-Mantel-Haenszel test for repeated measures was used to evaluate effect of treatment. These observations included: "panting" (used as an event due to sample size and frequency), "yawning" (frequency), and "locomotion". A mixed regression model, with dog identity as a random factor, was used to evaluate the relationship between the collar mounted accelerometer counts as a measure for activity and the observational data on percentage time spent "mobile" ("exploration" + "locomotion"), time spent "immobile" and "other" ("non-visible" and "other").

II.4 Results

II.4.1 Body Temperature

A positive and significant effect was found of baseline values on post-treatment values (dogs receiving placebo or medication at 90 minutes) ($P < 0.0001$). There was no significant effect of sequence ($P = 0.90$). These two results suggest that dogs allocated to Sequence 1 (placebo; medication) and Sequence 2 (medication; placebo) did not differ in temperature values overall and that post-treatment temperature values needed to be corrected with baseline values (baseline temperatures predicted post-treatment temperatures). There was no significant effect of medication (0.2 mg/kg dextroamphetamine) on body temperature with all sequences confounded ($P = 0.18$). In Sequence 1 (placebo; medication) there was no significant effect ($P = 0.39$) of medication; however in Sequence 2 (medication; placebo), the medicated temperatures were 0.13°C higher than the mean temperature of the placebo group ($P = 0.016$). (Figure 4).

II.4.2 Heart rate

Results show there is a significant effect of medication (0.2 mg/kg dextroamphetamine) on heart rate, with the medicated groups heart rates (mean = 99.07 bpm, SEM = 4.3128) being significantly ($P = 0.044$) lower than placebo group (mean = 112.35 bpm, SEM = 4.3128) (Figure 5). The results do indicate that although as a group the medicated dogs showed a significantly lower heart rate than the placebo group, individual dogs showed variability in heart rate (seven dogs showed more than 15 % decrease in heart rate, the decrease ranging from 16 to 34%; one dog showed more than 15 % decrease regardless of treatment). This effect of medication was independent of the sequence ($P = 0.81$). There was no significant effect of baseline values on post-treatment heart rate values

(P = 0.11) and no significant effect of sequence (P = 0.54). These two results indicate that individuals allocated to the two sequences of treatments, Sequence 1 (placebo; medication) and Sequence 2 (medication; placebo) did not differ in heart rate values overall and that post-treatment heart rate values did not need to be corrected with baseline values.

II.4.3 Video analysis

II.4.3.1 Percentage of time spent "immobile"

The results show that there was no significant effect of treatment (P = 0.11); dogs receiving dextroamphetamine 0.2 mg/kg did not spent more or less time "immobile" when compared to dogs receiving placebo. These results were independent of the sequence of treatments (P = 0.39). Baseline values predicted post-treatment values significantly (P = 0.001) but they were not affected by sequence (P = 0.16) and so post-treatment values needed to be corrected for baseline values.

II.4.3.2 Percentage time spent "exploring"

There was no significant effect of treatment (P = 0.11) and these results were independent of the sequence of treatments (P = 0.35). Baseline values predicted post-treatment values significantly (P = 0.001) but they were not affected by sequence (P = 0.26) and so post-treatment values needed to be corrected for baseline values.

II.4.3.3 Frequency of "locomotion"

"Locomotion" was not very frequently observed and so the data were analyzed as prevalence (did the dog move or not during the observation time). The Cochran-Mantel-Haenszel test for repeated measures indicated that the prevalence of locomotion did not differ statistically between the two treatments ($P = 0.48$). Pre-treatment prevalence also did not differ statistically between groups ($P = 0.41$).

II.4.3.4 Frequency of "lip-licking"

There was no significant effect of treatment ($P = 0.89$) and the results were independent of the sequence of treatments ($P = 0.47$). Baseline values predicted post-treatment values significantly ($P = 0.02$) but they were not affected by sequence ($P = 0.09$) and so post-treatment values needed to be corrected for baseline values.

II.4.3.5 Frequency of "panting"

"Panting" was not very frequently observed and so the data were analyzed as a prevalence (did the dog pant or not during the observation time). The Cochran-Mantel-Haenszel test for repeated measures indicates that the prevalence of "panting" did not differ statistically between the two treatments (placebo and medicated) ($P = 1$). This was also the case for the frequency of "panting" in pre-treatment groups. "Panting" appeared to be less prevalent in the two post-treatment groups (a decrease from 66.7% to 16.7%).

II.4.3.6 Frequency of "yawning"

The Cochran-Mantel-Haenszel test for repeated measures indicated that the prevalence of yawning did not differ statistically between the two treatments ($P = 0.08$). Pre-treatment prevalence also did not differ statistically between groups ($P = 0.32$).

II.4.4 Accelerometer

II.4.4.1 Motor activity

Figure 6 displays an example of raw data of activity counts in a 60 minute period for one test subject. Results show there was no significant effect of treatment (0.2 mg/kg dextroamphetamine) with all sequences confounded ($P = 0.52$). The accelerometer counts for pre-treatment placebo (116.52 ± 120) and medicated (97.75 ± 54.73) groups were higher than the post-treatment placebo (62.30 ± 54.39) and medicated (45.70 ± 41.48) groups (Figure 7). Baseline values predicted post-treatment values significantly ($P = 0.0001$) but they were not affected by sequence ($P = 0.09$) and so post-treatment values needed to be corrected for baseline values.

II.4.4.2 Comparison between the accelerometer and observational motor activity data

Results show there was a strong relationship between the accelerometer counts measured and the observational percentage time spent "mobile' ("exploration" + "locomotion") ($P < 0.0001$) (Figure 8). There was an inverse relationship between time spent "immobile" and activity count's ($P < 0.0001$).

II.5 Discussion

This study demonstrates that Beagle dogs receiving one oral dose of 0.2 mg/kg of dextroamphetamine do not show significant changes in body temperature, specific behaviors such as "lip-licking", "panting", "yawning", and motor activity. The marginal increase in temperature of medicated dogs in Sequence 2 (medication; placebo), may be due to chance, or may in fact be representative of changes seen in other studies [17,18] where normal Beagle dogs had increased mean body temperature 0.5 - 1 hour after administering 0.75 - 2.0 mg/kg of oral dextroamphetamine.

"Panting" frequency in both post-treatment groups was reduced from 66.7% to 16.7%. This result may simply display habituation effect.

The results do show that although as a group the medicated dogs presented a significantly lower heart rate than the placebo group, individual dogs showed variability in heart rate. This variability would suggest that a low dose dextroamphetamine test resulting in decreased heart rate in Beagles may in fact not identify truly hyperkinetic dogs. It is also possible that some of these dogs (Beagles) are true "responders" to amphetamines. Dogs may be considered "responders" or "non-responders" to treatment with amphetamines, based on early studies using the Telomian-Beagle hybrid dog as an endogenous model of Hyperkinetic Syndrome in children.[18, 19] These studies described behavioral changes at high doses of dextroamphetamine in both control and hybrid dogs. These Telominan-Beagle hybrid dogs had been shown to exhibit hyperactivity, impulsiveness and impaired learning.

When Corson and Corson[20] attempted to train the Telomian-Beagle dogs in a Pavlovian stand either with positive or negative reinforcement they found variability in response to treatment with dextroamphetamine. At doses of 1.2 - 2.0 mg/kg, the hybrid dogs could be differentiated into two groups: "responders" and "non-responders". The "responder" dogs displayed marked improvement after administration of dextroamphetamine in the inhibitory field test (a modified sit-stay test) and did not have the hyperthermic or stereotypic responses of the control Beagle dogs and "non-responder" hybrid dogs.[18,20] Further studies on these hybrid dogs showed that there may be neurochemical differences between the "responders" and "non-responders". "Non-responder" dogs were found to have defects in dopamine receptors at the post-synaptic level and so were not sensitive to the action of amphetamine. In the case of the "responders" the dopamine defect was at the pre-synaptic level and so they were responsive to amphetamines.[18] These studies show that HS may be determined on a polygenic basis and that each individual dog may have different neurochemical defects that lead to the expression of the same behavioral signs.[18,19,21]

The response of dogs in our study to a low oral dose of dextroamphetamine may have been influenced by multiple factors such as the individual dogs' neurochemistry, the dose of stimulant given, as well as the amount of time allotted to evaluate drug effect. In previous studies[18], increased body temperature and stereotypic behaviors of control Beagles at 2.0 mg/kg (high dose) were notable and peaked at 0.5 - 1 hour and 6 - 6.5 hours respectively after administration. Stereotypic behaviors in this study were described as those consisting of repetitive walking forward and backward, jerking movements such as head wagging, and circling. These Beagles had peak plasma amphetamine levels at 1.5

hours post administration.[21] It is hypothesized by several authors[2,6,16] that dogs that do not suffer from HS will exhibit typical autonomic arousal such as increased arousal and activity, increased heart and respiratory rates and possibly hyperthermia, tremors and anorexia when challenged with amphetamines.

Dextroamphetamine at oral doses of 1 - 2 mg/kg could induce various stereotyped behaviors, including head bobbing, circling, pacing and sniffing.[2,17] A recent study by Tontodonati et al.[17] discovered that Beagle dogs receiving low oral doses of dextroamphetamine (between 0.25 – 0.75 mg/kg) did not have significant change in their heart rates 1 – 20 hours after treatment. However at higher doses of 1.5 mg/kg the Beagle dogs displayed an increase in heart rate. The Tontodonati et al[17] study contradicts our findings, since a lower dose of 0.2 mg/kg did cause a significant reduction in heart rate in our study Beagle dogs. Frequency of heart rate monitoring, method of monitoring and length of monitoring may account in part for differences between these studies. Tontodonati et al[17] monitored heart rate on a continuous basis using an implanted ECG electrode telemetry device whereas our study used a Polar® heart rate monitor.

In a practical sense, it is very difficult to study behavior in dogs in their natural home environment. It may be seen as intrusive and very time-consuming. As reported in other studies[13,14] the use of the accelerometer in this study was shown to be a reliable tool for measuring motor activity in the dog. Nearly 83% of the variation in the activity counts could be predicted using observed time spent “mobile”. When comparing the activity counts with time spent “unknown” (“unknown = “other” and “non-visible”) there was a

positive relationship between the measures. Only 21% of the variation in the accelerometer counts could be predicted using "unknown" values which indicate that certain body movements may or may not be recorded as activity counts depending on the accelerometers' minimal threshold setting. Yamada and Tokuriki[14] found that at lower thresholds, such as 0.02G, more subtle movements (head movements) were recorded by the accelerometer. The accelerometers used in veterinary research are presently small in size and the collar mounted location has been found to be the most reliable location on the dog.[13] Other objective methods for measuring motor activity such as grid-line tests [22,23] and pedometers have been used.[24] The reliability of these measures however is questionable. In a study by Chan et al.[24] pedometers and owner-reported activity were correlated ($r = 0.305$) but it was also noted that pedometer accuracy differed with both size and gait of the dog.

Both in human and animal studies, the accelerometer does not provide any information regarding co-ordination of movements, the purposefulness, appropriateness or the goal directedness of the activity it is recording. Regardless of its shortcomings, objective measures such as the accelerometer can be used as an adjunct to conventional subjective diagnostic tools including rating scales and observational studies.

Recently, a 13 item rating scale questionnaire was developed for dog owners to measure attention deficit and activity-impulsivity in their dogs and its validity and reliability were measured.[25] This questionnaire was primarily developed as a "tool for describing the typical responses of pet dogs to common stimuli in their natural environment". Although the study indicates that this questionnaire is both valid and

reliable, it does not however test for different raters other than the owners. As in human studies[26], there may be poor concordance between raters and this should be investigated further with this specific canine rating scale. The possible use of this type of rating scale in conjunction with amphetamine response tests could perhaps allow for a more comprehensive evaluation and diagnosis of HS in dogs.

II. 6 Conclusion

Based on the results in this study, the response to dextroamphetamine challenge in a dog is not likely to be a diagnostic tool for hyperkinesis. It is also possible that non-HS dogs may respond physiologically to amphetamines in a similar way as truly HS dogs respond. If this were in fact true, the diagnostic criteria used in the amphetamine challenge response test presently described in behavior reference texts and publications would not be valid for diagnosis of HS. If a dog responds paradoxically to amphetamines, it may in fact, simply respond to treatment with amphetamines (i.e. be a responder).

Beagle dogs in this study did not display any significant changes in body temperature, motor activity and certain specific behaviors such as “lip-licking”, “panting” and “yawning” within 90 minutes of receiving an oral dose of 0.2 mg/kg of dextroamphetamine. The heart rate of the studied Beagle dogs was significantly reduced with treatment as is seen in a paradoxical response indicating that a low dose oral dextroamphetamine challenge test may in fact not identify truly hyperkinetic dogs. This test would simply reveal “responders” to this drug.

The accelerometer is a reliable tool to measure motor activity in dogs.

II.7. References

1. Campbell WE. Behavioral modification of hyperkinetic dogs. *Modern Veterinary Practice* 1973; 54: 49-52.
2. Crowell-Davis S. *Veterinary Psychopharmacology*. Blackwell Publishing. Ames, Iowa. 2006; 166-178.
3. Houpt, KA. Domestic Animal Behavior for Veterinarians and Animal Scientists 4th Ed. Blackwell Publishing, 2005; 114-117.
4. Landsberg G., Hunthausen W, Ackerman W. *Handbook of Behavior Problems in the Dog and the Cat*. Saunders, Edinburgh. 2003: 140-141 and 319-320.
5. Lindsay SR. Etiology and Assessment of Behavior Problems In: *Handbook of Applied Dog Behavior and Training*. Iowa: Iowa State University Press. 2001; 147-158.
6. Overall KL. *Clinical Behavioral Medicine for Small Animals*. Mosby, Missouri 1997: 269-310.
7. Goddard ME., Beilharz RG. The relationship of fearfulness to, and the effects of sex, age and experience on exploration and activity in dogs. *Applied Animal Behaviour Science* 1984; 12: 267-278.
8. Hennessy MB., Voith VL., Mazzei SJ., Buttram J., Miller DD., Linden F. Behavior and cortisol levels of dogs in a public animal shelter, and an exploration of the

ability of these measures to predict problem behavior after adoption. *Applied Animal Behaviour Science* 2001; 73: 217-233.

9. Hsu Y., Serpell JA., Development and validation of a questionnaire for measuring behavior and temperament traits in pet dogs. *Journal of the American Veterinary Medical Association* 2003; 223; 1293-1300.
10. Jones CJ., Gosling SD. Temperament and personality in dogs (*Canis familiaris*): A review and evaluation of past research. *Applied Animal Behaviour Science* 2005; 95: 1-53.
11. Campbell WE. Behavior Problems in Dogs 2nd Ed. American Veterinary Publications. Goleta, California. 1992; 129-140.
12. Luescher A. Hyperkinesis in dogs: six case reports. *Canadian Veterinary Journal.* 1993; 34: 368-370.
13. Hansen BD., Lascelles D., Kene BW., Adams AK., Thomson AE. Evaluation of an accelerometer for at-home monitoring of spontaneous activity in dogs. *American Journal of Veterinary Research* 2007; 68: 468-475.
14. Yamada M., Tokuriki M. Spontaneous activities measured continuously by an accelerometer in Beagle dogs housed in a cage. *Journal of Veterinary Medical Science* 2000; 62(2): 443-447.
15. Roden DM. Chapter 5. Principles of Clinical Pharmacology. In: Fauci AS, Braunwalk E, Kasper DL, et al., eds. *Harrison's Principles of Internal Medicine*. 17 ed. McGraw-Hill Publishing Co. 2008.
16. Baggot JD., Davis LE., A comparative study of the pharmacokinetics of amphetamine. *Research in Veterinary Science* 1973; 14(2): 207-215.

17. Tontodonati M., Fasdelli N., Moscardo E., Giarola A., Dorigatti R. A canine model used to simultaneously assess potential neurobehavioural and cardiovascular effects of candidate drugs. *Journal of Pharmacological and Toxicological Methods* 2007; 56(2): 265-275.
18. Bareggi SR, Becker RE, Ginsburg B, et al. Paradoxical effect of amphetamine in an endogenous model of the hyperkinetic syndrome in a hybrid dog: Correlation with amphetamine and *p*-hydroxyamphetamine blood levels. *Psychopharmacology*. 1979; 62: 217-224.
19. Bareggi SR, Becker RE, Ginsburg BE, et al. Neurochemical investigation of an endogenous model of the "hyperkinetic syndrome" in a hybrid dog. *Life Sciences*. 1979; 24: 481-488.
20. Corson SA, Corson EO'L. Constitutional differences in physiological adaptation to stress and distress. In: Serban G ed. *Psychopathology of Human Adaptation.* New York, Plenum Press, 1976; 77-94.
21. Bareggi SR, Gomeni R, Becker R.E. Stereotyped behavior and hyperthermia in dogs: Correlation with the levels of amphetamine and p-hydroxyamphetamine in plasma and CSF. *Psychopharmacology*. 1978; 58:89-94.
22. Hennessy MB, Voith VL, Mazzei SJ, et al. Behavior and cortisol levels of dogs in a public animal shelter, and an exploration of the ability of these measures to predict problem behavior after adoption. *Applied Animal Behaviour Science.* 2001; 73: 217-233.

23. Wilson E, Sundgren P-E. Behaviour test for eight-week old puppies – heritability's of tested behaviour traits and its correspondence to later behaviour. *Applied Animal Behaviour Science.* 1998; 58: 151-162.

24. Chan CB, Spierenburg M, Ihle SL, et al. Use of pedometers to measure physical activity in dogs. *Journal of the American Veterinary Medical Association*. 2005; 226(12): 2010-2015.

25. Vas J, Topál J, Péch E, et al. Measuring attention deficit and activity in dogs: A new application and validation of a human ADHD questionnaire. *Applied Animal Behaviour Science*. 2007; 103: 105-117.

26. Mitsis EM, McKay KE, Schulz KP, et al. Parent- teacher concordance for DSM-IV attention-deficit hyperactivity disorder in a clinic-referred setting. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2000; 330-339.

---

a. Polar® Heart Rate monitor, Polar Electro Oy, Kempele, Finland.

b. Observer® Noldus Information Technology Inc. Leesburg, VA, USA.

c. Actical®, Lynx Scientific Equipment Inc., Montreal, Quebec, Canada

---

II. 8 Table Legend

Table I. Behavioral categories and specific behaviors for observational video analysis

Behavioral Categories*	Behaviors#	Description
Activity	**Immobile**	Immobile sitting down, lying down, immobile standing, or immobile stand-2-pelvic (standing on 2 pelvic limbs)
	Locomotion	Walking or running around without exploring the environment (pacing)
	Exploration	Any activity directed toward physical aspects of the environment, including sniffing, close visual inspection and gentle oral examination such as licking
	Not-Visible	
	Other	Any behavior not previously described within this category including shaking and scratching body parts.
Facial	**Panting**	Rapid and shallow breathing with mouth open
	Not-Panting	Normal breathing, mouth closed
	Yawning (Event)	Yawning
	Lip-licking (Event)	Tongue out and licking lips, nose or face. Tongue seen.

***** The behavioral categories are not mutually exclusive.

All behaviors are state (duration) variables except for lip licking and yawning in the category of facial. All behaviors within each category are mutually exclusive with the exception of behaviors recorded as event.

II. 9 Figure Legend

Figure 1: Placebo controlled cross-over study design.

Diagram of study design displaying Sequence 1 (placebo; medicated) and Sequence 2 (medicated; placebo) in a cross-over design.

Figure 2: Photograph of dog wearing neck-mounted Actical® accelerometer.

Photograph of dog wearing an activity monitor used to detect body movements in dogs This unit contains an omni-directional accelerometer which is sensitive to movement in all directions at a minimal force of 0.1G. It is most sensitive to movement in the direction parallel with the longest dimension of the accelerometer case (horizontal in the case of the dog carrying it on his neck). Voltage generated by the sensor is amplified and filtered by analog circuitry and then converted within a microprocessor to create a digital value. Photograph thanks to Bio-Lynx Scientific Equipment Inc., Montréal, Québec, Canada.

Figure 3: Photograph of study dog wearing a chest mounted Polar® Heart Monitor.

Heart beats per minute were collected every 5 seconds over the duration of the study periods. The results were downloaded to a computer after each 1.5 hour testing period.

Figure 4: Effect of treatment (0.2 mg/kg dextroamphetamine) and placebo on mean body temperature in both sequences as measured in degrees Celsius.

This figure displays the effect of 0.2 mg/kg oral dextroamphetamine on the Beagle dog's rectal body temperature as measured in degree Celsius°. The 2 Sequences on the y axis represent: Sequence 1 (placebo; medicated) and Sequence 2 (medicated; placebo).

Figure 5: Box plot of the effect of 0.2 mg/kg of oral dextroamphetamine on heart rate.

Lines within each box show the median and the box extends from the 25^{th} and 75^{th} percentile. Bards extend from the boxes to reach 1.5 times the interquartile range and dots are data points beyond this range.

Figure 6: Example of 60 minutes of activity counts collected using the Actical® accelerometer.

Example of raw activity scores from one subject during a one hour period within the study. The accelerometer unit was selected as 15 seconds. Every 15 seconds the voltage generated within the accelerometer is compressed and converted into an integer and reported as an activity count. The data was downloaded to a computer by placing the Actical® unit into a telemetric reader after each study period.

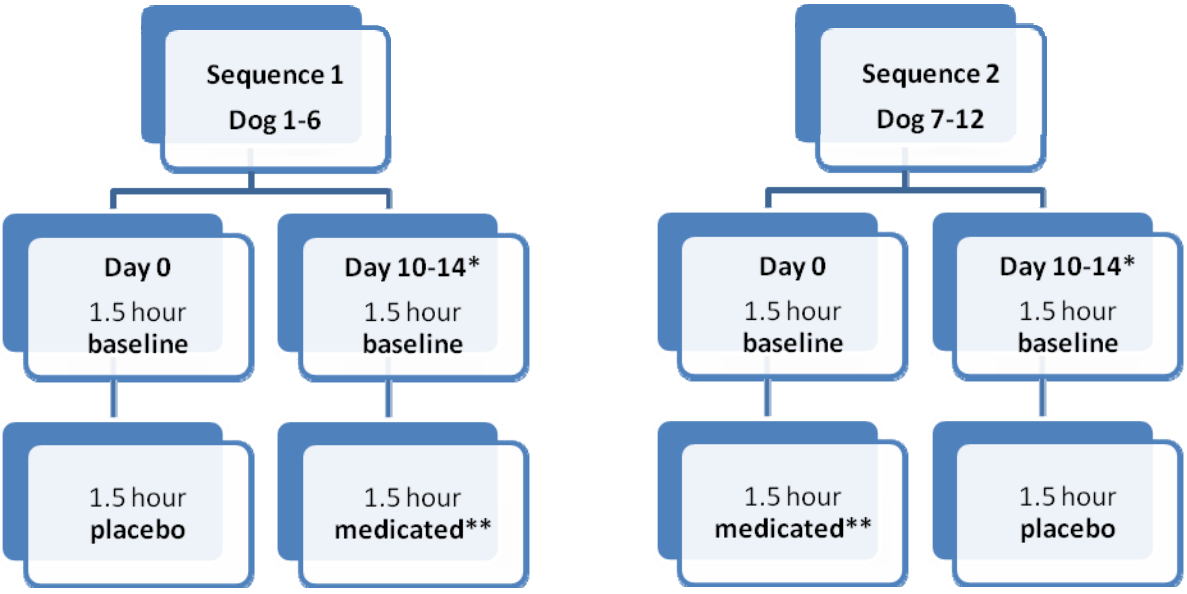
Figure 7: Average collar mounted activity counts / 15 seconds

Average collar mounted accelerometer counts / 15 seconds in all 4 groups including pre-treatment recorded activity. Treatment consisted of placebo or medication (0.2 mg/kg oral dextroamphetamine).

Figure 8: Correlation between time observational time spent "mobile" and collar mounted Actical® counts.

Correlation between the video observational time spent "mobile" (time spent "exploring" and time spent in "locomotion") and the collar mounted accelerometer activity counts.

Figure 1. Placebo Controlled Cross-over Study Design



* Days 10-14: Allowed time for adequate washout period.
** Medicated: Dogs receiving 0.2 mg/kg oral dextroamphetamine.

Figure 2. Photograph of dog wearing neck-mounted Actical® accelerometer.

Figure 3: Photograph of study dog wearing chest mounted Polar® Heart Monitor.

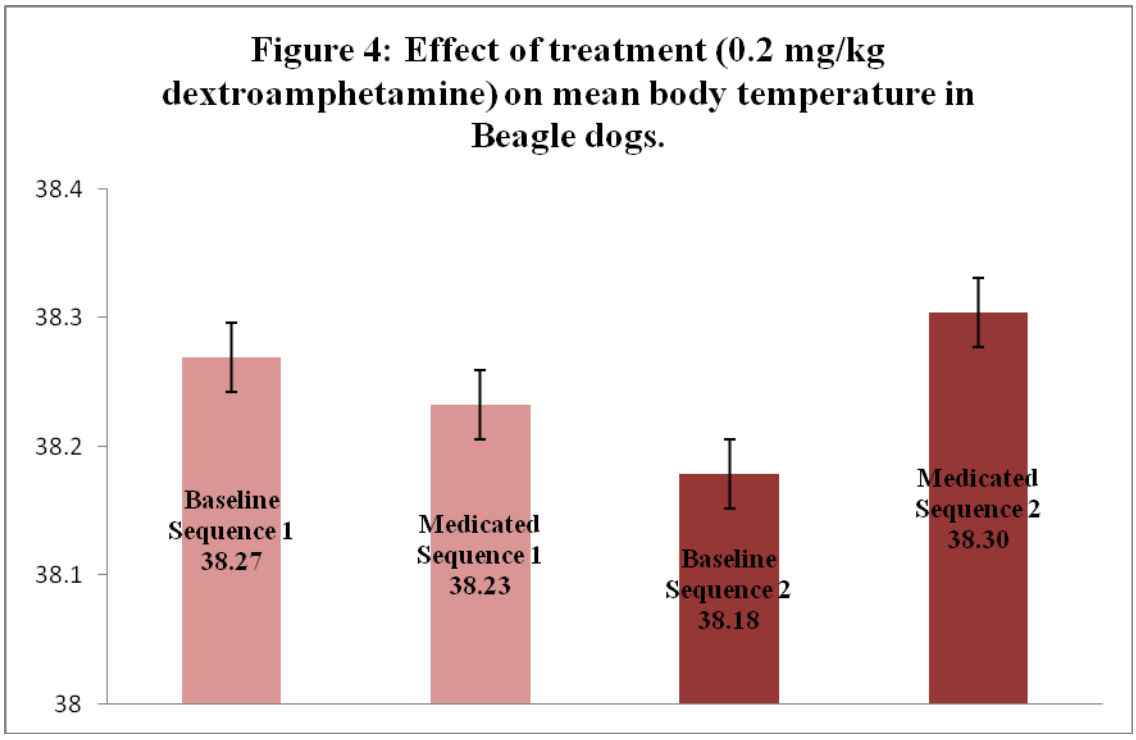


Figure 4: Dogs receiving 0.2 mg/kg of oral dextroamphetamine had no effect on mean body temperature within 90 minutes of treatment with all sequences confounded ($p = 0.18$). In Sequence 1 (placebo; medication) there was no significant effect of treatment ($p = 0.39$). In Sequence 2 (medication; placebo) there was a 0.13°C increase in mean body temperature in the medicated dogs ($p = 0.016$).

Figure 5. Box plot of the effect of 0.2 mg/kg oral dextroamphetamine on heart rate

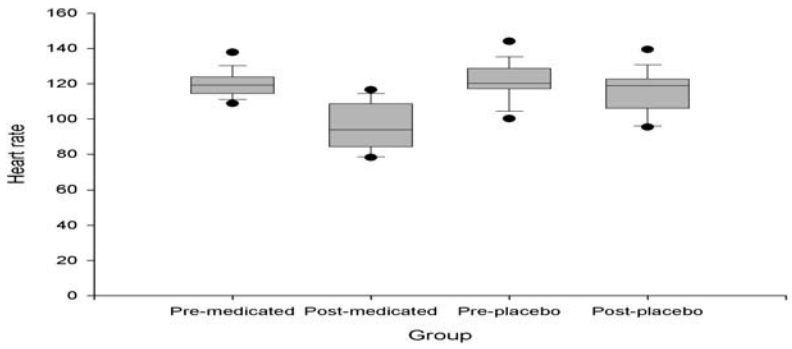


Figure 5: Box plot of the effect of 0.2 mg/kg of oral dextroamphetamine on heart rate. Lines within each box show the median and the box extends from the 25th and 75th percentile. Bards extend from the boxes to reach 1.5times the interquartile range and dots are data points beyond this range.

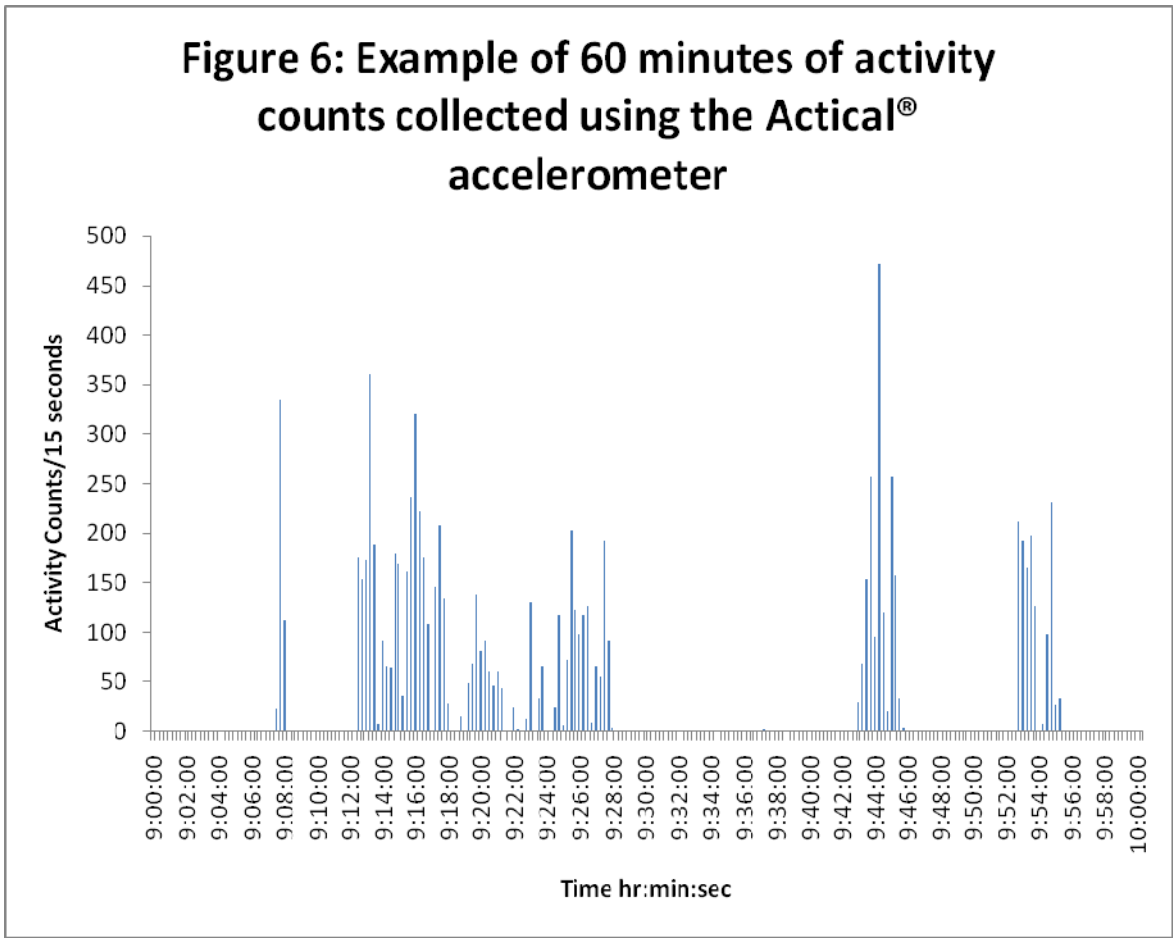


Figure 6: Example of 60 minutes of activity counts collected using the Actical® accelerometer
Activity Counts/15 seconds
500
450
400
350
300
250
200
150
100
50
0
9:00:00
9:02:00
9:04:00
9:06:00
9:08:00
9:10:00
9:12:00
9:14:00
9:16:00
9:18:00
9:20:00
9:22:00
9:24:00
9:26:00
9:28:00
9:30:00
9:32:00
9:34:00
9:36:00
9:38:00
9:40:00
9:42:00
9:44:00
9:46:00
9:48:00
9:50:00
9:52:00
9:54:00
9:56:00
9:58:00
10:00:00
Time hr:min:sec

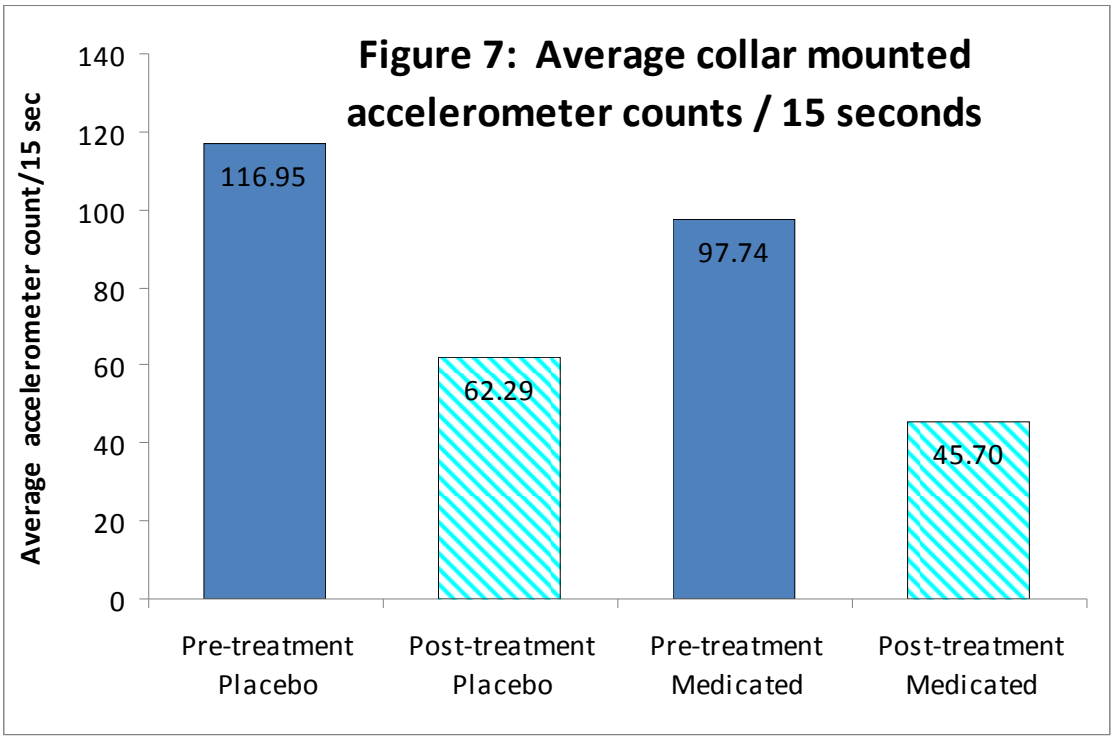


Figure 7: Treatment consisted of placebo or medicated (0.2 mg/kg dextroamphetamine). When post-treatment values were adjusted for baseline pre-treatment values, there was no significant difference between placebo and medicated groups ($p = 0.52$) with all sequences confounded.

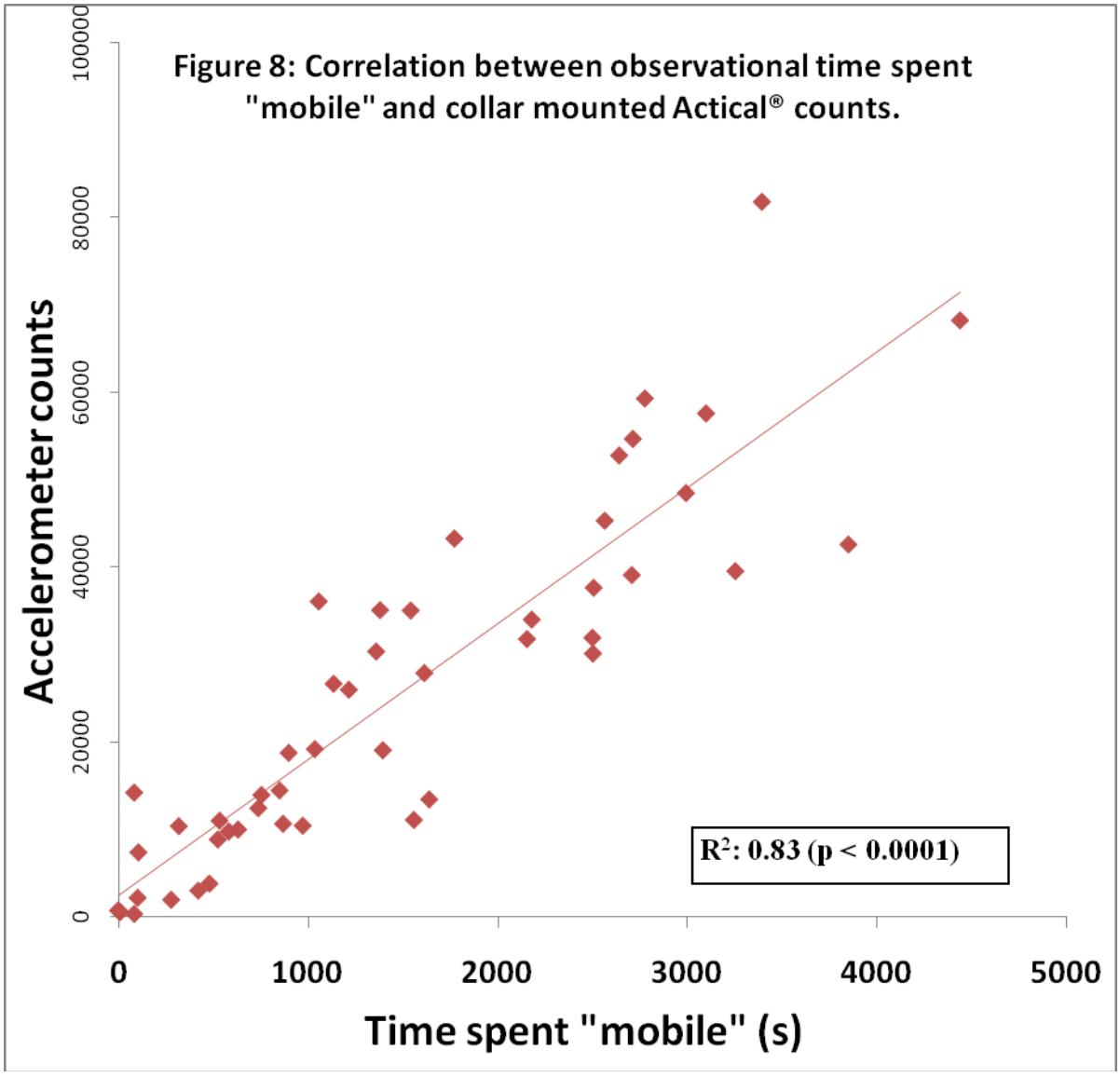


Figure 8: Correlation between observational time spent "mobile" and collar mounted Actical® counts.
Accelerometer counts
0
20000
40000
60000
80000
100000
0
1000
2000
3000
4000
5000
Time spent "mobile" (s)
R²: 0.83 (p < 0.0001)

Chapter III Discussion and Conclusion

III.1 General Overview

Veterinary clinical practitioners currently lack adequate diagnostic criteria and techniques for evaluating Hyperactivity or Hyperkinesis Syndrome (HS) in domestic dogs. Evidence-based tools for the identification and diagnosis of HS in practice are badly needed. It is the author's belief that proper diagnosis and treatment of dogs that truly suffer from HS would lead to fewer cases of euthanasia due to behavioural problems and an improved quality of life for those dogs and their caregivers.

The key research question which this thesis attempts to answer is: How do we identify dogs as suffering from HS if we do not know what constitutes a 'normal' activity level in the dog population? The current diagnostic practice for this syndrome uses a single response test which could easily lead to misdiagnosis.

The dextroamphetamine response test described in Chapter I and originally developed in the 1970s was designed using a very specific group of dogs: the Telomian-Beagle hybrid dogs, which displayed certain clinical signs of "hyperkinesis" (Corson & Corson 1976). The test was then further investigated by Campbell (1973) using case-based trials of domestic owned dogs who appeared to display behaviours congruent with "hyperkinesis" (as defined at that time, see section I.1.5). The definitions and behavioural criteria being used in current clinical practice to identify dogs possibly suffering from HS vary amongst authors, leading to great debate in the field of veterinary behavioural medicine. Even the clinician's selection of which dogs should undergo the diagnostic

amphetamine response test is variable. We suggest that a primary clinical interpretation of dogs presenting with abnormal activity levels and/or inattention is not possible, given the significant lack of baseline data on 'normal' dog activity and attention.

In humans, the use of amphetamines to treat children and adults with Attention-Deficit Hyperactivity Disorder (ADHD) was a secondary development for treatment and amphetamines are not used as a primary method of diagnosis as they are in the veterinary literature. People suffering from ADHD must first be diagnosed with the disorder based on thorough diagnostic criteria such as that seen in the Conners Teacher Rating Scale (see I.1.3) (Annex I). Rating scales have only very recently been investigated in the veterinary literature and are not currently being used as a diagnostic tool for HS (Vas et al. 2007).

In section III.2, the clinical implication of the research study conducted will be discussed while in section III.3 and III.4, the limitations of the study and future research possibilities will be reviewed.

III.2 Clinical Implications

HS is defined as a syndrome. A syndrome is generally classified as a group of symptoms that collectively indicate or characterize a disease, psychological disorder, or other abnormal condition (American Psychiatric Association 1994). HS can be considered a syndrome because it does not have one compelling clinical sign associated with it but instead presents a group of symptoms. At present, however, diagnosis of HS in dogs is based mainly on the use of a single objective diagnostic response test on dogs that display some or all of a highly variable list of clinical behavioural signs.

In human medicine, hyperactivity is a central feature of ADHD (Attention-deficit Hyperactivity Disorder), and is usually defined as excessive or developmentally inappropriate levels of motor activity. The diagnostic criteria of ADHD have evolved in the past 30 years, as the lifestyles of children have changed dramatically requiring them to spend more time in classrooms and being inactive yet attentive for long periods of time. With an estimated 3-5% of all children in North America suffering from ADHD (Barkley 1996) there has been a great deal of research undertaken to understand the factors involved in this disorder, their proper diagnosis and treatment. There is now thus some question whether this disorder existed 100 years ago, when children in North America and the western world, spent most of their time doing physical activity rather than sitting in classrooms.

In human medicine, in contrast to veterinary medicine, response to amphetamines is not used as a diagnostic test in ADHD in children or adults. A double-blind cross-over study done in by Zhan et al. (1980) discovered that dextroamphetamine affected both normal and hyperactive boys in a similar way. Both groups of children showed on average reduced motor activity and impulsivity, improved attention and reduced heart rate prior to a reaction time task test.

Additionally, there remains much controversy over the possible over-diagnosis and over-treatment of ADHD with amphetamines among the general public and medical profession. The study by Zhan et al. (1980) in combination with clinical interpretations in the field, have led investigators and clinicians to question the abundant use of stimulants in the treatment of children with ADHD as there is likely a subgroup of children who truly do not have ADHD but still respond paradoxically to stimulants.

In the present study, similar results to the human clinical response were found: overall, Beagle dogs that were not displaying behavioural signs of HS responded in a paradoxical fashion with respect to heart rate. As an example, Beagle dog #9 was found to have a baseline average heart rate of 113 bpm. After receiving 0.2 mg/kg dextroamphetamine, the average heart rate during the following 90 minutes for this dog decreased to 77 bpm (a reduction of 33 percent). If this particular dog had been presented for behavioural evaluation in a veterinary clinic and a clinician followed the recommended amphetamine response test described by various authors (see section I.1.5), a misdiagnosis of canine HS could easily have been made.

In veterinary practice it would be unlikely that a clinician would attempt an amphetamine-response test in a dog that is not displaying any signs of HS behaviourally. Diagnostic behavioural criteria for HS in dogs are however vague and inconsistent in the literature. The combination of poor behavioural criteria and a diagnostic test that has not been based on scientific evidence may lead to dogs being inappropriately labelled as either "normal" or HS. It is possible that, as with some children, dogs may display certain 'paradoxical' changes when given amphetamines, even if behaviourally non-HS.

The use of objective measurements in combination with well designed rating scales may allow veterinary investigators the added advantage of further defining canine hyperactivity in terms of quantity and pattern rather than defining it categorically through an amphetamine response test. Currently available human diagnostic tools include rating scales (parent and/or teacher) (Conners 1969, Annex I) as well as other psychometric evaluations and in some cases the use of solid-state actigraphs, and pedometers to measure

the activity level of the person. Given that ADHD is among the most frequently diagnosed child psychiatric disorder (Barkley 1996) it is not surprising that human medical professionals are working towards establishing more objective methods of diagnosis.

There are currently a number of behavioural methods available to veterinarians. Until recently, most veterinary behaviourists used the published questionnaires and temperament tests of Goddard & Beilharz (1984), Hennessy et al. (2001) and Hsu & Serpell (2003). Categories and labels such as "Activity" (Goddard & Beilharz 1984), "Locomotor activity" (Hennessy et al. 2001) and "Excitability and Trainability" (Hsu & Serpell 2003) were used in these questionnaires and temperament tests. These subjective clinical evaluations were not well validated and most studies did not address validity issues.

In comparison, the new Vas et al. (2007) 13-item rating scale questionnaire was primarily developed as a "tool for describing the typical responses of pet dogs to common stimuli in their natural environment". With further investigation and validation, it is the author's hope that clinicians and behaviourists will be able to use this scale for improved diagnostic capabilities for HS and other behavioural problems, in preference to unreliable and potentially misleading amphetamine response tests.

Using remote devices such as the accelerometer may also reduce a researcher's time and energy significantly when studying motor activity in the dog. It allows researchers to use a quantifiable method to assess motor activity in the dog in many different environmental settings (home, office, kennel, etc). The accelerometers used in veterinary research are presently small in size, lightweight and in some cases, already collar mounted (as was the device used in this study). Using diagnostic criteria such as objective measures

of motor activity and validated rating scales in addition to response-tests, may improve the diagnostic capabilities of clinicians for HS.

In conclusion, the findings of this study suggest there is good reason to question the use of the diagnostic HS test in clinical practice. At 0.2 mg/kg, oral dextroamphetamine may cause Beagle dogs to display a paradoxical reduction in heart rate potentially leading to misdiagnosis of HS. It is clear that the definition of HS is highly variable and controversial even amongst veterinary behaviourists. This syndrome is clinically ill-defined and further investigation is needed. Validating current or new rating scales may assist in defining this syndrome. Studies using rating scales will allow for larger representative groups of dogs to be evaluated, improving the strength of these studies. Without baseline studies of motor activity and impulsive/attentive tendencies in the pet dog population, an accurate diagnosis of HS is impossible. In other words, a diagnosis of "abnormal" behaviour is suspect if we have not first defined "normal" behaviour.

Without a true definition and clear diagnostic clinical signs, veterinary behaviourists may simply refer to dogs that respond paradoxically to amphetamines as "amphetamine responsive". Instead of this test being a diagnostic test, it is in reality more of a treatment trial. Are the dogs that respond paradoxically to dextroamphetamine truly HS? From our present study, we can extrapolate that some Beagle dogs may respond paradoxically even when not behaviourally HS (using the current behavioural clinical signs associated with HS in the literature).

III.3 Limitations of the Study

III.3.1 Study Design and Methodology

III.3.1.1. Dose of Dextroamphetamine and Length of Monitoring

The responses resulting from the low doses of 0.2 mg/kg dextroamphetamine on the study Beagle dogs may have been influenced by the dose of stimulant given, as well as the amount of time allotted to evaluate effect. It is possible that had higher doses of dextroamphetamine been used very different effects of treatment on the study dogs may have been seen. Behavioural effects of dextroamphetamine in humans are increased by larger doses. Over the course of a given dose, however, there is a divergence between such behavioural effects and drug concentration in the blood (Angrist et al. 1987). In particular, behavioural effects peak before maximal blood levels are reached, and decline as blood levels remain stable or even continue to increase.

Results could also have been influenced by length of time the test dogs were monitored and data collected. The decision to take measurements up to 90 minutes after the dogs received medication was based on the previously described amphetamine response test (see section I.1.5). As mentioned in the introduction of this thesis, the original study design included a dosing regime of both 0.2 mg/kg and one of 1.3 mg/kg dextroamphetamine. The first dog to receive the higher dose of 1.3 mg/kg displayed stereotypic behaviours 3.5 hours after receiving the oral dose (personal communication, Dr Diane Frank). For reasons of animal welfare, the higher dose regimen was discontinued. Although this observation was of a single dog, prior publications suggest that higher doses

such as 0.75 - 2.5 mg/kg are likely to cause significant neurobehavioral effects including stereotypies and vocalizations (Bareggi et al. 1978; Tontodonati et al. 2007).

In our study the marginal increase in body temperature of medicated dogs in Sequence 2 (medication; placebo) may have been due to chance, or may in fact be representative of changes seen in other studies. Other studies have used higher doses of dextroamphetamine and monitored the changes in body temperature over a greater length of time. Bareggi et al. (1979a) suggested that there was a significant increase in mean body temperature 0.5 – 1 hr after administering 2.0 mg/kg of dextroamphetamine. Tontodonati et al. (2007), noted an increase in body temperature (up to 1.2 and 2.5 °C) when dosing dogs at 0.75 and 1.5 mg/kg dextroamphetamine respectively. The effect of these higher doses was observed between 0.5 and 10 hr after dosing and peaked at 2 hr post-dose (Tontodonati et al. 2007). Prior publications suggest that there is a dose-dependent effect of dextroamphetamine on body temperature and that as the dose of dextroamphetamine administered increases, so too may body temperature (Bareggi et al. 1979; Tontodonati et al. 2007). Our study did not investigate more than one dose of dextroamphatemine, so we were unable to test a possible dose dependent effect.

Previous studies also suggest that there is a dose dependent effect on heart rate. Results from Tontodonati et al. (2007), suggested that heart rates may increase significantly at doses of 1.5 mg/kg, between 1 - 20 hrs after oral dosing and that lower doses such as 0.25 and 0.75 mg/kg will not cause a significant change in heart rate. If the heart rate increases significantly when giving an amphetamine, it suggests a direct and positive chronotropic effect on the cardiovascular system of that animal. Contrary to Tontodonati's

study (using 0.25 mg/kg oral dextroamphetamine), the present study displayed a significant effect of a low dose of dextroamphatemine (0.2 mg/kg) on heart rate in studied Beagle dogs.

With respect to changes in motor activity as a result of our tested low-dose of dextroamphetamine, there was no change in motor activity (video-recorded or by accelerometer) in the Beagle dogs. These results are similar to findings of Tontodonati et al. (2007) which suggested that Beagle dogs receiving doses of 0.25 mg/kg did not have any significant change in locomotion as measured by an implanted telemetry device or with observational video recordings. At higher doses of 0.75 mg/kg and 1.5 mg/kg, the Tontodonati et al. (2007) study showed that dogs would have an increase in locomotion between 2 to 5 hours post dosing. It is important to note that although the Tontodonati et al. (2007) study used a very small sample size (4 dogs) it was, to the author's knowledge, the first study performed that objectively evaluated the effect of dextroamphetamine on motor activity in the research Beagle.

III.3.1.2 Observational Descriptions and Specific Behaviours

In this study, specific behaviours were selected for observation based on their possible use as indicators of stress or anxiety. "Lip-licking", "yawning" or "panting" are three specific behaviours studied in this trial. However it is recognized that stress and anxiety are not the exclusive emotional or physiological factor behind the frequency or occurrence of dogs lip-licking, yawning or panting. For example, stress, anxiety, ambient temperature, and activity may all lead to an increase in frequency of panting. Stress, nausea and anxiety may all lead to lip-licking (Beerda et al. 1998). None of these behaviours has

been previously studied in dogs receiving dextroamphetamine or other amphetamines and so it is difficult to comment on the likelihood of changes in these behaviours (frequency or duration) when the dogs are subjected to dextroamphetamine. It is possible that if dogs at higher doses of dextroamphatemine tended to show more excitement and vocalizations/stereotypies (Bareggi et al. 1978; Tontodonati et al. 2007), then we could extrapolate that these dogs would display an increase in frequency and/or duration of stress induced behaviours such as panting and yawning. Panting could also be increased in dogs with greater environmental and body temperatures, a factor that was not investigated for effect.

The behavioural categories in this study were defined prior to any observations of the study dogs. The stated variables of locomotion and exploration were found to be difficult to differentiate at times during video observation. For example, when the subject dog's head was facing away from the camera, it was unclear as to whether he/she was goal directed (exploration) or not. For this reason and due to low frequency of the locomotion behaviour, both "locomotion" and "exploration" were combined to form time spent "mobile" for the purposes of analysis of activity data.

III.3.1.3 Beagles as Study Subjects and the Possible Influence of Heritability and Genetics on HS and ADHD

The present study used research Beagle dogs to help control for variations between breeds and other environmental factors. This homogeneity of subjects allowed for ease of data collection and analysis. Using this type of study subject group, however, made it

difficult to compare with other studies and to extrapolate results found in the general dog population of owned dogs.

This homogeneity of study subjects is found in many other comparative studies investigating the effect of amphetamines on dogs. Beagle dogs raised for research purposes may not however be representative of the owned domestic dog population both behaviourally and physiologically. Using a cohort of subjects from a variety of breeds, ages, and sexes of domestic owned dogs would have provided the study with a better representation of the pet dog population seen in clinical practice. This type of clinical study however, would be difficult to repeat and validate given the gene-environment interaction seen in the pet population described recently (Hejjas et al. 2007). Using pet dogs for pharmacological research, especially with potentially harmful medications such as dextroamphetamine, is ethically questionable and does not support animal welfare. Using Beagles allowed us to control for many environmental factors and complete an early investigation on the use of dextroamphetamine in diagnostic testing of HS.

A recent publication by Hejjas et al. (2007) studied the association between the dopamine D4 receptor gene (DRD4) polymorphism and activity-impulsivity scores (using the 13-item rating scale mentioned in section I.1.3.1) in a single breed population (200 German Shepherd dogs). In humans, DRD4 variable number of tandem repeats (VNTR) is thought to be related to ADHD (Faraone et al. 2005). In dogs, a similar repeat polymorphism in DRD4 gene has been suggested by Niimi et al. (1999).

The question as to whether behaviour traits such as aggression, excitability, and activity are heritable and/or due to variations in the DRD4 gene has been the focus of recent canine studies (Niimi et al. 1999; Hejjas et al. 2007). In children, the heritability of ADHD has been estimated to be as high as 80% (Thapar et al. 2000). To the author's knowledge, there are no studies on the heritability of HS in dogs. Given the veterinarian's perceived rarity of HS in the pet dog population and the variability of criteria used to diagnose this syndrome, the lack of research on this subject is not surprising.

Results from Hejjas et al. (2007), found that DRD4 VNTR polymorphism was associated with the activity-impulsivity score of an environmentally homogeneous group of police dogs. The same investigation was performed using a population of pet German Shepherd's and this genetic association with activity–impulsivity scores was not found (Hejjas et al. 2007). It is clear from this study that there is an important interaction between genetics and environment when investigating this DRD4 polymorphism. The environmental interactions (nutrition, housing, relationships, etc), may affect the phenotypic expression of dogs with this polymorphism. This polymorphism in a German Shepherd dog is not necessarily predictive of an elevated activity-impulsivity score (and perhaps dogs suffering from HS). Future studies investigating other breeds and factoring for specific environmental factors are needed.

Age and sex of subjects in the present study were not factored into the analysis. An equal male-to-female ratio was used in the study and all dogs were within 13 - 20 months of age. To the author's knowledge, there has been no objective research performed investigating age or sex in dogs with respect to incidence of HS or of the effects of

amphetamines on these differing ages or sexes. Other studies such as those done by Tontodonati et al. (2007) and Bareggi et al. (1979a) used very small cohorts of subjects and did not do factor analysis with age or sex. In humans, ADHD is seen more commonly in boys than it is in girls (Barkley 1996). Vas et al. (2007) found that juvenile dogs (10 - 24 months of age) qualified as being more inattentive than adult dogs using an owner rated 13-item scale. This same study found no significant difference between inattention in male and females. Male juvenile dogs however were found to have a tendency (but not significant) to have higher "activity-impulsivity" scores.

III.3.1.4 Measuring Activity: Observational versus the Accelerometer

The use of the accelerometer in this study, as in others (Yamada & Tokuriki 2000; Hansen et al. 2007), suggests that it is a reliable tool for measuring motor activity in the dog. Observational activity studies are both intrusive and very time-consuming and laborious. Other objective methods for measuring motor activity such as grid-line tests (Wilson & Sundgren 1998; Hennessy et al. 2001) and pedometers have been used (Chan et al. 2005). For instance pedometers and owner-reported activity were correlated at ($r = 0.305$) in a study by C.B. Chan et al. (2005). It was however found that pedometer accuracy differs with both size of the dog and the dog's gait (Chan et al. 2005). Hansen et al. (2007) demonstrated that the accelerometer correlates positively with video-graphic measurements of movement and mobility in dogs with a weight ranging between 18kg - 28kg.

Despite these advantages, the accelerometer (in both human and animal studies) does not provide any information regarding the level of co-ordination of movements, their

purposefulness or appropriateness, or the goal directedness of the activity recorded, which may be important information for the researcher. In the present study, there were some difficulties with proper categorization of “locomotion” and “exploration”. This could have been improved upon if the observer understood the goal directedness of the studied activity. The accelerometer, for instance, would not have assisted in quantifying these types of behaviours or stereotypies as they would appear simply as an increase in motor activity. Underlying emotional or behavioural response is also not measurable by the accelerometer.

III.4 Future Studies

It is evident from the above discussion that there is a need for more research in the field of canine motor activity, inattention and impulsivity. Can we objectively assess baseline motor activity, inattention and impulsivity in dogs? What is the normal amount of motor activity in the pet dog population? What is the normal attention span of a dog? Do factors such as breed, size of dog, age, environment, or lifestyle or a combination of all these factors affect motor activity and attention? Large cohort, multi-factor, multi-disciplinary studies are needed, such as those seen in human studies.

Accelerometer motor activity studies on the owned pet dog population in the home and hospital environment would give veterinarians and the public some baseline data on the “normal” motor activity of pet dogs. If these proposed studies were used in conjunction with the newly published 13-item activity and impulsivity rating scale in Vas et al. (2007),

it may allow for the development of reliable and validated diagnostic criteria for dogs suffering from true HS.

III.5 Overall Conclusion

As the new specialty of veterinary behavioural medicine grows in North America, so should the advancement and promotion of evidence-based behavioural medicine. Currently dogs that are presented to veterinary clinicians with suspected Hyperactivity or Hyperkinesis Syndrome are evaluated against a list of clinical signs that are considered to be typical criteria for this syndrome in dogs. These clinical signs, as discussed section II, are varied, inconsistent and controversial. There is little evidence to date as to the diagnostic validity of these clinical signs and whether certain factors, such as age, breed, sex, genetics and environment play a role. Moreover, if a dog displays certain or all of these clinical signs, then the clinician may perform a further diagnostic test using an amphetamine-response regimen as recommended in most veterinary behavioural texts and manuals.

The primary objective of this thesis was to examine the reliability of the amphetamine-response test. The rationale behind this test is that dogs responding "typically" to amphetamines will show either an increase or no change in physiological responses such as heart rate, respiratory rate and motor activity. Conversely, a decrease of these parameters suggests a paradoxical response in the aforementioned markers, indicating that the dog suffered from HS.

In this study, when the effects of 0.2 mg/kg oral dextroamphetamine were measured on behaviourally non-HS Beagle dogs, we expected to see either no change or a stimulant effect as described above. The present study suggests however that this assumption may not be true in all cases or for all the markers as the test dogs showed a significant reduction in heart rate with this low-dose of oral dextroamphetamine. These results are contradictory to other studies, which have suggested that at such low-doses of dextroamphetamine, Beagle dogs should not show any significant change in heart rate.

The veterinary literature assumes that dogs which respond paradoxically to dextroamphetamines are in fact, suffering from HS. However the dogs in this study displayed no clinical signs of HS despite a paradoxical reduction in heart rate. This unexpected result is in fact similar to that found in human studies, where a number of children who are not clinically ADHD respond paradoxically to amphetamines, suggesting that this test may not a reliable indicator of HS in dogs.

In conclusion, it is recommended that the amphetamine response test for HS be used with caution and as only one of many diagnostic tools for the veterinarian. Alternatively, the amphetamine response test could be used clinically as a treatment trial to determine appropriate drug therapy for behaviourally hyperactive, hyper-stimulated, or over-active dogs. In this case, researchers will need to quantifiably measure what is “normal” motor activity, and also what constitutes inattention and impulsivity for the pet dog, as there is presently no normative data against which to measure any “abnormal” activity observed in a clinical or laboratory settings.

In time, the newly published 13-item activity and impulsivity rating scale in conjunction with other more objective tools to measure activity in the dog (such as those used in this study) may provide the necessary information needed for the development of reliable and validated criteria for diagnosing HS.

Bibliography

Allen, D.G., Dowling, P.M., Smith, D., Pasloske, K & Woods, J. 2004. Handbook of Veterinary Drugs. 3rd Edition. pp. 190-191. Philadelphia NY: Willey-Blackwell.

American Psychiatric Association. 1968. Diagnostic and Statistical Manual of Mental Disorders, 2nd Edition (DSM II). Washington, D.C.: American Psychiatric Association.

American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV). Washington, D.C.: American Pschiatric Association.

Angrist, B., Corwin, J., Bartlik, B. & Cooper, T. 1987. Early pharmacokinetics and clinical effects of oral D-amphetamine in normal subjects. Biological Psychiatry, 22**,** 1357-1368.

Arnold, L.E., Kirilcuk,V., Corson, S.A. & Corson, E.O. 1973. Levoamphetamine and dextroamphetamine: differential effect on aggression and hyperkinesis in children and dogs. American Journal of Psychiatry, 130**,** 165-170.

Baggot, J.D. & Davis, L.E. 1973. A comparative study of the pharmacokinetics of amphetamine. Research in Veterinary Science, 14**,** 207-215.

Bareggi, S.R., Becker, R.E., Ginsburg, B. & Genovese, E. 1979a**.** Paradoxical effect of amphetamine in an endogenous model of the hyperkinetic syndrome in a hybrid dog: correlation with amphetamine and p-hydroxyamphetamine blood levels. Psychopharmacology (Berl), 62**,** 217-224.

Bareggi, S.R., Becker, R.E., Ginsburg, B.E. & Genovese, E. 1979b. Neurochemical investigation of an endogenous model of the "hyperkinetic syndrome" in a hybrid dog. Life Sciences, 24**,** 481-488.

Bareggi, S.R., Gomeni, R. & Becker, R.E. 1978. Stereotyped behavior and hyperthermia in dogs: correlation with the levels of amphetamine and p-hydroxyamphetamine in plasma and CSF. Psychopharmacology (Berl), 58**,** 89-94.

Barkley, R.A. 1996. Attention-Deficit Hyperactivity Disorder. In: Child Psychopathology (Ed. by E.Marsh & R.A.Barkley), pp. 63-112. New York: Guilford Press.

Beerda, B., Schilder, M.B.H., Van Hooff, J.A.R.A.M., & de Vries, H.W. 1998. Behavioural, saliva cortisol and heart rate responses to different types of stimuli in dogs. Applied Animal Behavioural Science, 58, 365–381.

Brunner, D., Buhot, M.C., Hen, R. & Hofer, M. 1999. Anxiety, motor activation, and maternal-infant interactions in 5HT1B knockout mice. Behavioral Neuroscience, 113, 587-601.

Campbell, W.E. 1973. Behavioral modification of hyperkinetic dogs. Modern Veterinary Practice, 54**,** 49-52.

Campbell, W.E. 1992. Physiology and Behavior. In: Behavior Problems in Dogs. 2nd Edition. (Ed. by P.W. Pratt), pp. 129-140. Goleta, California: American Veterinary Publications.

Canadian Pharmacists Association 2007. Compendium of Pharmaceuticals and Specialties. 42nd Edition. pp. 707-708.

Chan, C.B., Spierenburg, M., Ihle, S.L. & Tudor-Locke, C. 2005. Use of pedometers to measure physical activity in dogs. Journal of the American Veterinary Medical Association, 226**,** 2010-2015.

Conners, C.K. 1969. A teacher rating scale for use in drug studies with children. American Journal of Psychiatry, 24**,** 149-154.

Conners, C.K. 1990. Conners' Rating Scales Manual. 2nd Edition. Toronto: Multi-Health Systems Inc.

Corson, S.A. & Corson, E.O. 1976. Animal models of violence and hyperkinesis. In: Animal Models in Human Psychobiology (Ed. by G.Serban & A.King) New York: New York Plenum Press.

Corson, S.A., Corson, E.O., Becker, R.E., Ginsburg, B., Trattner, A., Connor, R.L., Lucas, L.A., Panksepp, J. & Scott, J.P. 1980. Interaction of genetics and separation in canine hyperkinesis and in differential responses to amphetamine. The Pavlovian Journal of Biological Science, 15**,** 5-11.

Crowell-Davis, S. & Murray, T. 2006. CNS Stimulants. In: Veterinary Psychopharmacology. pp. 166-178. Ames, Iowa: Blackwell Publishing.

Dane, A.V., Schachar, R.J. & Tannock, R. 2000. Does actigraphy differentiate ADHD subtypes in a clinical research setting? Journal of the American Academy of Child & Adolescent Psychiatry, 39**,** 752-760.

Dehasse, J. Clinical management of stereotypies and overactivity in dogs. Proceedings of the Second World Meeting on Ethology. 1999. Lyon, France.

Diniz, P.P., Sousa, M.G., Gerardi, D.G. & Tinucci-Costa, M. 2003. Amphetamine poisoning in a dog: case report, literature review and veterinary medical perspectives. Veterinary and Human Toxicology, 45**,** 315-317.

Faraone, S.V., Perlis, R.H., Doyle, A.E., Smoller, J.W., Gorlanick, J.J., Holmgren, M.A. & Sklar, P. 2005. Molecular genetics of attention-deficit/hyperactivity disorder. Biological Psychiatry, 57, 1313-1323.

Gainetdinov, R.R., Wetsel, W.C., Jones, S.R., Levin, E.D, Jaber, M. & Caron, M.G. 1999. Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. Science, 283, 397-401.

GlaxoSmithKline. Dexedrine® Label insert. 2006. Research Triangle Park, NC. Reference Type: Pamphlet.

Goddard, M.E. & Beilharz, R.G. 1984. The relationship of fearfulness to, and the effects of sex, age and experience on exploration and activity in dogs. Applied Animal Behaviour Science, 12**,** 267-278.

Halperin, J.M., Matier, K., Bedi, G., Sharma,V. & Newcorn, J.H. 1992. Specificity of inattention, impulsivity and hyperactivity to the diagnosis of attention-deficit hyperactivity disorder. Journal of the American Academy of Child & Adolescent Psychiatry, 31**,** 190-196.

Hansen, B.D., Lascelles, B.D., Keene, B.W., Adams, A.K. & Thomson, A.E. 2007. Evaluation of an accelerometer for at-home monitoring of spontaneous activity in dogs. American Journal of Veterinary Research, 68**,** 468-475.

Hejjas, K.,Vas, J., Topal, J., Szantai, E., Ronai, Z., Szekely, A., Kubinyi, E., Horvath, Z., Sasvari-Szekely, M. & Miklosi, A. 2007. Association of polymorphisms in the dopamine D4 receptor gene and the activity-impulsivity endophenotype in dogs. Animal Genetics, 38, 629-633.

Hennessy, M.B., Voith, V.L., Mazzei, S.J., Buttram, J., Miller, D.D. & Linden, F. 2001. Behaviour and cortisol levels of dogs in a public animal shelter, and an exploration of the ability of these measures to predict problem behavior after adoption. Applied Animal Behaviour Science, 73**,** 217-233.

Houpt, K.A. 2005. Domestic Animal Behavior for Veterinarians and Animal Scientists. 4th Edition. pp. 114-117, Ames, Iowa: Blackwell Publishing.

Hsu, Y. & Serpell, J.A. 2003. Development and validation of a questionnaire for measuring behavior and temperament traits in pet dogs. Journal of the American Veterinary Medical Association, 223**,** 1293-1300.

Jones, C. & Gosling, S. 2005. Temperamant and personality in dogs (Canis familiaris): A review and evaluation of past research. Applied Animal Behaviour Science, 95**,** 1-53.

Kaplan, H.I. & Sadock, B.J. 1993. Pocket Handbook of Psychiatric Drug Treatment. pp.168-174, Baltimore, Maryland: Williams and Wilkin.

Kuczenski, R., Segal, D.S., Cho, A.K. & Melega, W. 1995. Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral responses to the stereoisomers of amphetamine and methamphetamine. Journal of Neuroscience, 15**,** 1308-1317.

Landsberg, G., Hunthausen, W. & Ackerman, W. 2003. Handbook of Behavior Problems in the Dog and the Cat. pp. 140-141 & 319-320, Edinburgh: Saunders.

Lascelles, B.D., Hansen, B.D., Thomson, A., Pierce, C.C., Boland, E. & Smith, E.S. 2008. Evaluation of a digitally integrated accelerometer-based activity monitor for the measurement of activity in cats. Veterinary Anesthesia and Analgesia, 35**,** 173-183.

L**indsay, S.R.** 2001. Handbook of Applied Dog Behavior and Training: Etiology and Assessment of Behavior Problems. pp. 147-158, Iowa: Iowa State University Press.

Lindsay, S.R. 2003. Handbook of Applied Dog Behavior and Training: Procedures and Protocols. pp. 256-278, Iowa: Blackwell Publishing.

Luescher, U.A. 1993. Hyperkinesis in dogs: Six case reports. Canadian Veterinary Journal, 34**,** 368-370.

Mitsis, E.M., McKay, K.E., Schulz, K.P., Newcorn, J.H. & Halperin, J.M. 2000. Parent-teacher concordance for DSM-IV attention-deficit/hyperactivity disorder in a clinic-referred sample. Journal of the American Academy of Child & Adolescent Psychiatry, 39**,** 308-313.

Niimi, Y., Inoue-Murayama, M., Murayama, Y., Ito, S., & Iwasaki, T. 1999. Allelic variation of the *D4 dopamine receptor* polymorphic region in two dog breeds, Golden retriever and Shiba. Journal of Veterinary Medical Sciences, 62, 1281-1286.

Overall, K.L. 1997. Clinical Behavioral Medicine for Small Animals. pp. 269 & 310. Missouri: Mosby.

Pageat, P. 1998. Pathologie Du Comportement Du Chien. pp.267-363. Paris, France: Édition du PointVétérinaire.

Patrick, K. & Markowitz, J. 1998. Pharmacology of methylphenidate, amphetamine enantiomers and pemoline in attention-deficit hyperactivity disorder. Human Psychopharmacology: Clinical and Experimental, 12**,** 527-546.

Patronek, G.J., Moyer, M.R., & Glickman, L.T. 1995. Population dynamics and risk of euthanasia for dogs in an animal shelter. Anthrozoos, 8, 31-43.

Patronek, G.J., Glickman, L.T., Beck, A.M., McCabe, G.P. & Ecker, C. 1996. Risk factors for relinquishment of dogs to an animal shelter. Journal of the American Veterinary Medical Association, 209, 572-581.

Randrup, A. & Munkvad, I. 1967. Stereotyped activities produced by amphetamine in several animal species and man. Psychopharmacologia, 11**,** 300-310.

Risner, M.E. & Jones, B.E. 1979. The effects of psychomotor stimulants on single-spatial alternation behavior in dogs. Psychopharmacology (Berl), 63**,** 137-141.

Serpell, J.A. & Hsu, Y. 2001. Development and validation of a novel method for evaluating behavior and temperament in guide dogs. Applied Animal Behaviour Science, 72**,** 347-364.

Siwak, C.T., Tapp, P.D., Zicker, S.C., Murphey, H.L., Muggenburg, B.A., Head, E., Cotman, C.W. & Milgram, N.W. 2003. Locomotor activity rhythms in dogs vary with age and cognitive status. Behavioral Neuroscience, 117**,** 813-824.

Stowe, C.M., Werdin, R.E., Barnes, D.M., Higbee, J., Miller, J., Knoll, L.W., Dayton, R.M. & Sittig, D.C. 1976. Amphetamine poisoning in dogs. Journal of the American Veterinary Medical Association, 168**,** 504-506.

Teo, S.K., Stirling, D.I., Thomas, S.D., Evans, M.G. & Khetani, V.D. 2003. A 90-day oral gavage toxicity study of d-methylphenidate and d,l-methylphenidate in beagle dogs. International Journal of Toxicology, 22**,** 215-226.

Thapar, A., Harrington, R., Ross, K., & McGuffin, P. 2000. Does the definition of ADHD affect heritability? Journal of the American Academy of Child & Adolescent Psychiatry, 39, 1528-1536.

Tontodonati, M., Fasdelli, N., Moscardo, E., Giarola, A. & Dorigatti, R. 2007. A canine model used to simultaneously assess potential neurobehavioural and cardiovascular effects of candidate drugs. Journal of Pharmacological and Toxicological Methods, 56**,** 265-275.

Tryon, W.W. & Pinto, L.P. 1994. Comparing activity measurements and ratings. Behavior Modification, 18**,** 251-261.

Vas, J., Topal, J., Pech, E. & Miklosi, A. 2007. Measuring attention deficit and activity in dogs: A new application and validation of a human ADHD questionnaire. Applied Animal Behaviour Science, 103**,** 105-117.

Volkow, N.D., Wang, G.J., Newcorn, J., Telang, F., Solanto, M.V., Fowler, J.S., Logan, J., Ma, Y., Schulz, K., Pradhan, K., Wong, C. & Swanson, J.M. 2007. Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention deficit/hyperactivity disorder. Archives of General Psychiatry, 64, 932-40.

Voith, V.L. 1980a. Play behavior interpreted as aggression or hyperactivity: case histories. Modern Veterinary Practice, 61**,** 707-709.

Voith, V.L. 1980b. Hyperactivity and hyperkinesis. Modern Veterinary Practice, 61**,** 787-788.

Wallach, M.B., Angrist, B. & Gershon, S. 1971. The comparison of the stereotyped behavior-including effects of d-and l-amphtemaine in dogs. Communications in Behavioral Biology. Part A., 6**,** 93-96.

Wilson, E. & Sundgren, P.-E. 1998. Behaviour test for eight-week old puppies – heritabilities of tested behaviour traits and its correspondence to later behaviour. Applied Animal Behaviour Science, 58**,** 151-162.

Yamada, M. & Tokuriki, M. 2000. Spontaneous activities measured continuously by an accelerometer in beagle dogs housed in a cage. Journal of Veterinary Medical Science, 62**,** 443-447.

Zahn, T.P., Rapoport, J.L. & Thompson, C.L. 1980. Autonomic and behavioral effects of dextroamphetamine and placebo in normal and hyperactive prepubertal boys. Journal of Abnormal Child Psychology, 8**,** 145-160.

Annex I

Subsection IV of the Conners' Teacher Rating Scale – Revised (S)

Conners' Teacher Rating Scale - Revised (S)

by C. Keith Conners, Ph.D.

Child's Name:_____ **Gender: M F**

Birthdate:____/____/____ (Month / Day / Year) **Age:**_____ **School Grade:**_____

Teacher's Name:_____ **Today's Date:**____/____/____ (Month / Day / Year)

Instructions: Below are a number of common problems that children have in school. Please rate each item according to how much of a problem it has been in the last month. For each item, ask yourself, "How much of a problem has this been in the last month?", and circle the best answer for each one. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to each item.

		NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
1.	Inattentive, easily distracted	0	1	2	3
2.	Defiant	0	1	2	3
3.	Restless in the "squirmy" sense	0	1	2	3
4.	Forgets things he/she has already learned	0	1	2	3
5.	Disturbs other children	0	1	2	3
6.	Actively defies or refuses to comply with adults' requests	0	1	2	3
7.	Is always "on the go" or acts as if driven by a motor	0	1	2	3
8.	Poor in spelling	0	1	2	3
9.	Cannot remain still	0	1	2	3
10.	Spiteful or vindictive	0	1	2	3
11.	Leaves seat in classroom or in other situations in which remaining seated is expected	0	1	2	3
12.	Fidgets with hands or feet or squirms in seat	0	1	2	3
13.	Not reading up to par	0	1	2	3
14.	Short attention span	0	1	2	3
15.	Argues with adults	0	1	2	3
16.	Only pays attention to things he/she is really interested in	0	1	2	3
17.	Has difficulty waiting his/her turn	0	1	2	3
18.	Lacks interest in schoolwork	0	1	2	3
19.	Distractibility or attention span a problem	0	1	2	3
20.	Temper outbursts; explosive, unpredictable behavior	0	1	2	3
21.	Runs about or climbs excessively in situations where it is inappropriate	0	1	2	3
22.	Poor in arithmetic	0	1	2	3
23.	Interrupts or intrudes on others (e.g., butts into others' conversations or games)	0	1	2	3
24.	Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
25.	Fails to finish things he/she starts	0	1	2	3
26.	Does not follow through on instructions and fails to finish schoolwork (not due to oppositional behavior or failure to understand instructions)	0	1	2	3
27.	Excitable, impulsive	0	1	2	3
28.	Restless, always up and on the go	0	1	2	3

Conners' Teacher Rating Scale - Revised (S)

by C. Keith Conners, Ph.D.

Child's Name:_____ **Gender: M F**

Birthdate:____/____/____ (Month / Day / Year) **Age:**_____ **School Grade:**_____

Teacher's Name:_____ **Today's Date:**____/____/____ (Month / Day / Year)

For each item, transfer the circled number into each of the white boxes across the row. Sum each column and write the totals in the boxes at the bottom.

A. Oppositional	B. Cognitive Problems/ Inattention	C. Hyperactivity	D. ADHD Index
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			0 1 2 3
			TOTALS

Scale Descriptions

A. Oppositional
Individuals scoring high on this scale are likely to break rules, have problems with persons in authority, and are more easily annoyed and angered than most individuals their own age.

B. Cognitive Problems/Inattention
High scorers may be inattentive. They may have more academic difficulties than most individuals their age, have problems organizing their work, have difficulty completing tasks or schoolwork, and appear to have trouble concentrating on tasks that require sustained mental effort.

C. Hyperactivity
High scorers have difficulty sitting still, feel more restless and impulsive than most individuals their age, and have the need to always be on the go.

D. Conners' ADHD Index
Identifies children/adolescents "at risk" for ADHD.

Profile for Males: Conners' Teacher Rating Scale - Revised (S)

Child's Name:_____ **Gender: M F** (Circle One)

Birthdate:____/____/____ (Month / Day / Year) **Age:**____ **School Grade:**____

Teacher's Name:_____ **Today's Date:**____/____/____ (Month / Day / Year)

	A. Oppositional					B. Cognitive Problems/ Inattention					C. Hyperactivity					D. Conners' ADHD Index				
T	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
90																				
89																				
88																				
87																				
86																				
85																				
84																				
83																				
82																				
81																				
80																				
79																				
78																				
77																				
76																				
75																				
74																				
73																				
72																				
71																				
70																				
69																				
68																				
67																				
66																				
65																				
64																				
63																				
62																				
61																				
60																				
59																				
58																				
57																				
56																				
55																				
54																				
53																				
52																				
51																				
50																				
49																				
48																				
47																				
46																				
45																				
44																				
43																				
42																				
41																				
40																				
39																				
38																				

Note:
For age-groups:

Column 1: ages 3 to 5

Column 2: ages 6 to 8

Column 3: ages 9 to 11

Column 4: ages 12 to 14

Column 5: ages 15 to 17

Please see back of scoring sheet for Scale Descriptions

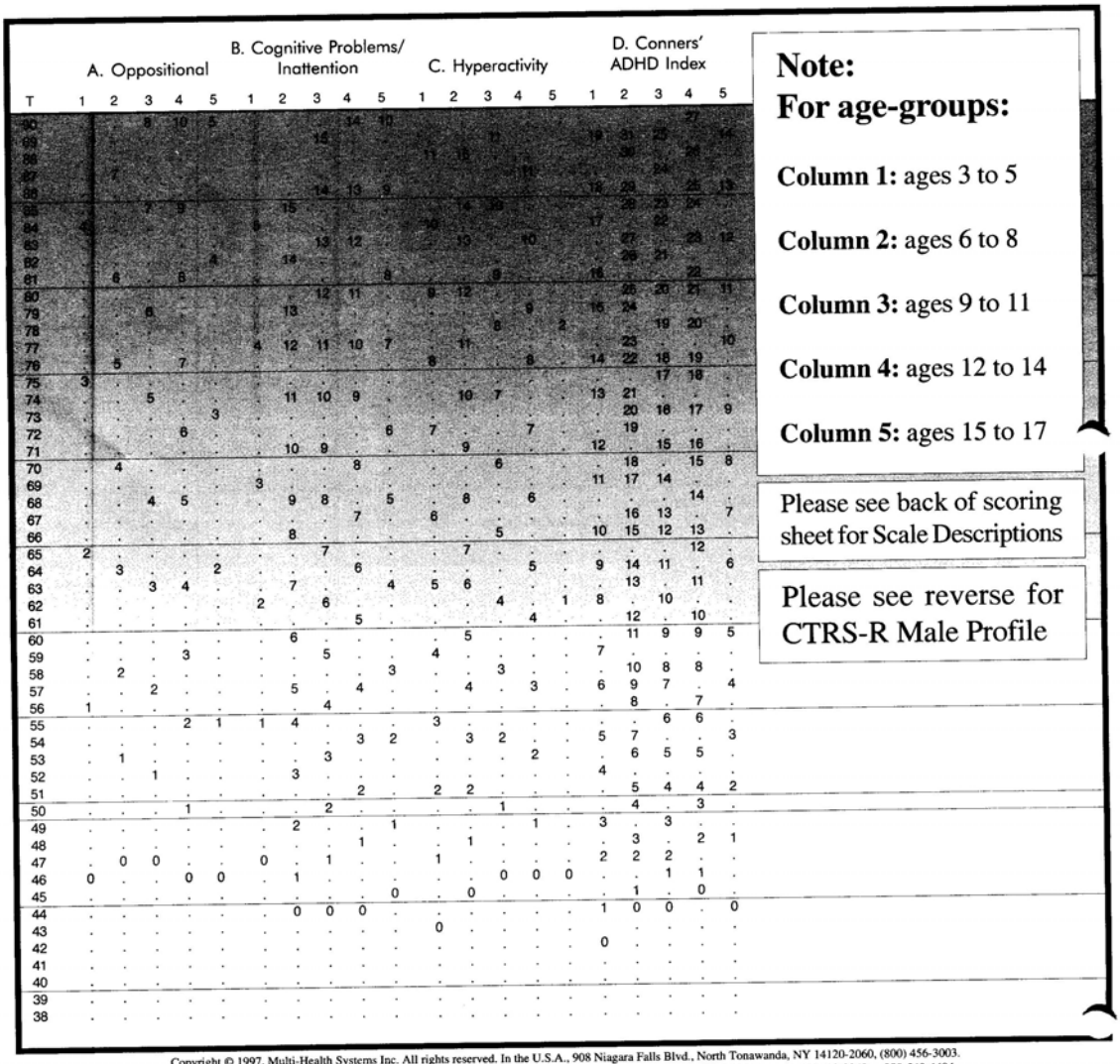
Please see reverse for CTRS-R Female Profile

Profile for Females: Conners' Teacher Rating Scale - Revised (S)

Child's Name:_____ **Gender: M F** (Circle One)

Birthdate:____/____/____ (Month / Day / Year) **Age:**____ **School Grade:**____

Teacher's Name:_____ **Today's Date:**____/____/____ (Month / Day / Year)



Note:
For age-groups:

Column 1: ages 3 to 5

Column 2: ages 6 to 8

Column 3: ages 9 to 11

Column 4: ages 12 to 14

Column 5: ages 15 to 17

Please see back of scoring sheet for Scale Descriptions

Please see reverse for CTRS-R Male Profile