Can we learn from human mental disorders to diagnose mental disorders in pets?

A thesis on the prevalence of obsessive-compulsive disorder and autism in companion animals

Master Thesis Behavioural Ecology

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Summary

In human medicine, many mental disorders have been described. To learn more about these mental disorders, animal models are often used[1]. These are often rodent models, in which the disorder has to be simulated. In domestic animals, such as dogs or cats, there is some behaviour resembling the behaviour we see in humans suffering from a mental disorder. So it might be, that domestic animals might also be suffering from mental disorders comparable to those seen in humans. Some scientists argue that we may learn more about human mental disorders by studying domestic animals that perform such behaviour[2]. To explore the applicability of domestic animals as models for human mental disorders, in this thesis, the following research question will be addressed: ‘‘Can we learn from human mental disorders to diagnose mental disorders in pets?”. Based on the existing literature, there appears to be an animal equivalent of Obsessive Compulsive Disorder (OCD), resembling the human disorder behaviourally and neurologically, but there is no convincing evidence for disorders which are more difficult to diagnose, such as autism, yet.

Abstract

In human medicine, many mental disorders have been described.To learn more about these mental disorders and the working mechanism behind them, many animal models are in use[1]. In most of these models, including rodent models, the disorder has to be simulated. Some of the behaviours of domestic animals seems to resemble mental disorders in humans. This brings up an interesting question. Since there appear to be resembling behavioural patterns in domestic animals, such as dogs and cats, do these animals then maybe also ‘suffer’ from mental disorders comparable to those as seen in humans? In fact, some scientists have argued that we may learn more about the biological basis of mental disorders by using domestic animals with naturally occurring behavioural symptoms as models[2]. To explore the applicability of domestic animals as models for human mental disorders, in this thesis, the following research question will be addressed: ‘‘Can we learn from human mental disorders to diagnose mental disorders in pets?” It is hypothesized that indeed some mental disorders are present in pets and that these mental disorders resemble the corresponding human mental disorder both behaviourally and neurobiologically. Based on literature, there appears to be an animal equivalent of OCD, resembling the human disorder behaviourally and neurologically, but there is no convincing evidence for disorders which are more difficult to diagnose, such as autism, yet.

1. Introduction

In human medicine, many mental disorders have been described. Most of these disorders are included in the “Diagnostic and Statistical manual of Mentaldisorders, also known as DSM, composed by the American psychiatric association. They define a mental disorder as following: “a clinically significant behavioural or psychological syndrome or pattern that occurs in an individual [which] is associated with present distress, or disability, or with a significant increased risk of suffering”[3]. They also state that mental disorders are not complete and discrete entities, and that there are no absolute boundaries between different mental disorders. The current DSM (DSM–IV–TR, 2000) lists 297 disorders[4], ranging from anxiety disorders to sexual disorders. The DSM is widely used to diagnose mental disorders in patients. It needs to be noted however, that even though it is a generally accepted manual, there is still some criticism. Most criticism regards the validity and reliability of the DSM[5, 6]. See for an elaborated discussion the papers of Pincus*et al.* (1998) and Kendell*et al.* (2003).

To learn more about these mental disorders and the working mechanism behind them, many animal models are in use[1]. There has been a lot of debate regarding the use of suchmodelsas in most of these models (rodents, nonhuman primates) the disorder has to be simulated, for example through brain lesions[1]. One of the major drawbacks of these models for the use of human psychiatry

is that there has been a lack of stable behavioural syndromes to study from social and biological perspective, in which rehabilitative approaches could have been tested[1].

Lately however, some scientists have argued that a better approach to determine the neurobiological and behavioural underpinnings of mental disorders might be to use domestic animals with naturally occurring behavioural symptoms as models[2]. Some of thebehaviours observed in domestic animals seem to resemble aspects of mental disorders in humans. These "natural" animal models could provide valuable insight in the perspective of human mental disorders[2]. Stein *et al.* (1994) suggested that if these disorders are studied, this could have significant theoretical and empirical implications for human psychiatry[2]. A number of examples are provided in their review article, such as *learned helplessness* as a model for depression, and narcolepsy in dogs and cats, which resembles narcolepsy in humans[2].

These new developments, of using domestic animals as natural models in human psychiatry, raise an interesting question. Since there appearto beresemblingbehavioural patterns in domestic animals, such as dogs and cats, do these animals then maybe also 'suffer' from mental disorders comparable to those as seen in humans? This question is gaining more and more interest amongst veterinarians and ethologists. There are some disorders that are more accepted to be present in domestic animals, such as narcolepsy in dogs and cats[7, 8] and obsessive compulsive disorder (OCD)[9].

However, some other mental disorders might be more difficult to diagnose in animals, since the mechanism of these diseases in humans is not yet fully understood, such as schizophrenia[10] and autism[11], and/or because the diagnostic possibilities are too limited at present. For instance, some disorders in humans are still mostly diagnosed based on 'behaviour', such as autism, and the diagnostic features used for humans might not always be applicable for animals.It is however very interesting to know if such disorders exist in animals, and if so, if they share a similar working mechanism or genetic basis.

The aim of this thesis is to assess the evidence for the occurrence of (possible) natural mental disorders in pets using knowledge from human mental disorders.The research question that is addressed in this thesis is :'Can we learn from human mental disorders to diagnose mental disorders in pets?' It is hypothesized that indeed some mental disorders are present in pets and that these mental disorders resemble the corresponding human mental disorder both behaviourally and neurobiologically.

Since too manymental disorders existto discuss in this thesis, the focus will be on two disorders, namely autism and Obsessive Compulsive Disorder (hereafter referred to as OCD). The reason for focusing on these two disorders is that recently a number of research groups focused on OCD in canines[9], which provided new insight in for example the genetics of OCD. Hence, it is very interesting to describe how OCD in pets such as canines and felines works, working down from the symptoms to the neurobiological working mechanism and the genetic background. As such, OCD in domestic animals provides a clear example of a mental disorder which is comparable in humans and (domestic) animals.

On the contrary, autism is a hardly describeddisorder in pets and the working mechanism remains largely unknown. Nevertheless, there is some ongoing research that suggests the possible occurrence of autism in (domestic) animals [9, 12]. In this thesis I will therefore also discuss the evidence for autism in pets, the behavioural evidence and possible biological mechanisms that accompany this disorder following the same systematic as will be applied for OCD.

So, the methodology of this thesis will be to describe these disorders on three different validity levels; face, predictive and construct validity. These three levels were composed to improve animal model validity. Robbins and Sahakian (1979) proposed to use the three validity levels mentioned above[13].Face validity is the behavioural similarity or the behavioural resemblance[14]. Predictive validity describes the pharmacological similarity between the animal model and the human disorder. Finally, construct validity refers to similarities in the underlying working mechanisms[14]. So the latter – construct validity – may be considered the highest level of validity that can be achieved for animal models[14].

Before discussing OCD and autism in pets, the symptoms and working mechanism (if this is known) of these disorders and the most common diagnose methods in humans will be discussed. This will be done by starting with the symptoms, and subsequently working down all the way to genetics, if feasible.Finally, these two human disorders are reflected on a resembling disorder known in pets. Their resemblance, diagnostic methods and eventually, their therapies will be compared with their human equivalent, and potentials will be discussed in more detail. This thesis will be completedwith some recommendations for future research on these disorders and other human mental disorders that might be of interest to study in domestic animals.

2. Obsessive compulsive disorder - Human

2.1.1 Obsessive Compulsive Disorder

Obsessive compulsive disorder has been defined by the Mayo foundation through the following definition: "An anxiety disorder characterized by unreasonable thoughts and fears (obsessions) that leads an individual to perform repetitive behaviours (compulsions)"[15]. The DSM-IV-TR has a more extensive definition for OCD. Their description of OCD is shown in scheme 1.
Briefly, DSM-IV-TR defines obsessions as"persistent ideas, thoughts, impulses, or images that are experienced as intrusive and inappropriate and that cause marked anxiety or distress"[3]. Compulsions are defined by the DSM-IV-TR as: "Repetitive behaviours (e.g., hand washing, ordering, and checking) or mental acts (e.g., praying, counting, and repeating words silently), the goal of which is to prevent or reduce anxiety or distress, and not to provide pleasure or gratification"[3]. In humans, the most frequent form of obsession is contamination (45%), and the most frequent occurring compulsion is checking (63%) followed by washing (50%)[16]. OCD is the fourth most frequent occurring psychiatric condition[16], and has a life time prevalence of 2.5 %, and an adult prevalence of 0.5% to 2.1%.[3]. The onset of this disorder is mostly at age 19 to 20[17]. Distribution of this disorder amongst males and females is about equal[18].

2.1.2 OCD and Stereotypies

It is important to realize that even though they might appear to be similar, OCD and stereotypic behaviour are not the same. The important difference between them is that in OCD the compulsive behaviour repeats an inappropriate goal, so the behaviour is "functional", such as washing your hands[19]. In stereotypies, the behaviour is the repetition of a certain not goal-directed motor pattern, such as repeating phrases, or hand flapping[20]. Apparently, different brain areas are associated to these two types of behaviour[20]: OCD has been connected with the prefrontal cortex, whereas stereotypies have been connected with the basal ganglia[20]. This topic will be discussed more extensively under the section of OCD in domestic animals.

Diagnostic criteria for 300.3 Obsessive-Compulsive Disorder

A. Either obsessions or compulsions:

- *Obsessions as defined by (1), (2), (3), and (4):*
  - recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress
  - the thoughts, impulses, or images are not simply excessive worries about real-life problems
  - the person attempts to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action
  - the person recognizes that the obsessional thoughts, impulses, or images are a product of his or her own mind (not imposed from without as in thought insertion)
- *Compulsions as defined by (1) and (2):*
  - repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly
  - the behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent or are clearly excessive

B. At some point during the course of the disorder, the person has recognized that the obsessions or compulsions are excessive or unreasonable. **Note:** This does not apply to children.

C. The obsessions or compulsions cause marked distress, are time consuming (take more than 1 hour a day), or significantly interfere with the person's normal routine, occupational (or academic) functioning, or usual social activities or relationships.

D. If another Axis I disorder is present, the content of the obsessions or compulsions is not restricted to it (e.g., preoccupation with food in the presence of an Eating Disorder; hair pulling in the presence of Trichotillomania; concern with appearance in the presence of Body Dysmorphic Disorder; preoccupation with drugs in the presence of a Substance Use Disorder; preoccupation with having a serious illness in the presence of Hypochondriasis; preoccupation with sexual urges or fantasies in the presence of a Paraphilia; or guilty ruminations in the presence of Major Depressive Disorder).

E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Scheme 1. OCD as described by the DSM-IV-TR (copy from DSM-IV-TR).

2.2 Diagnostics

A person can be diagnosed with OCD when he or she meets criteria A until E mentioned in scheme 1. So, in other words, a person may be diagnosed with OCD when: The person has obsessions or compulsions (A) that reoccur and are severe enough to be time consuming (more than 1 hour per day) or when these obsessions or compulsions cause distress of significant impairment (C). At some point the patient must recognize that his obsessions or compulsions are unreasonable or excessive (B). The behaviour of the patient is not due to direct physiological effects of a general medical condition or another substance, e.g. drugs or other medication (E). Also, if the patient is also suffering from another mental disorder, the content of his compulsions or obsessions are not restricted to this disorder (D).[3]

2.3 Working mechanism

An important factor in the pathophysiology of OCD is serotonin[89]. Serotonin, or 5-hydroxytriptamine, is a neurotransmitter[21]. This neurotransmitter plays a role in e.g. learning, mood and sleep[21]. It is also known to play a role in anxiety[21]. If the concentration of this neurotransmitter is altered in the brain, this can affect mood[21]. It is thought that serotonin plays an important role in OCD, which is summarized in the serotonin/5HT – hypothesis, which predicts that an abnormality of the serotonergic function in the brain is a critical factor for the development of OCD[17].
Indeed, several studies showed that serotonin reuptake inhibitors reduced obsessive compulsive behaviour[22, 23].

Dopamine, another neurotransmitter, is also thought to contribute to OCD[16]. Dopamine is a neurotransmitter which is involved in motor control and is a key neurotransmitter in the reward system[24]. It controls centers for reward and pleasure in the brain[24] and it is also involved in emotional responses and movement regulation[24]. This possible relation was shown in a study of McDougle*et al.* (1994), that revealed that the addition of dopamine antagonists was effective in reducing OCD symptoms where serotonin reuptake inhibitors (SRI's) alone did not have the desired effect[25].

However, there is still no exclusive answer to the exact molecular working mechanisms of this disorder. It is however likely that both dopamine and serotonin play an important role. Figure 1 shows three important neurotransmitters which can all affect mood and in several mental disorders drugs affecting these neurotransmitters are used.

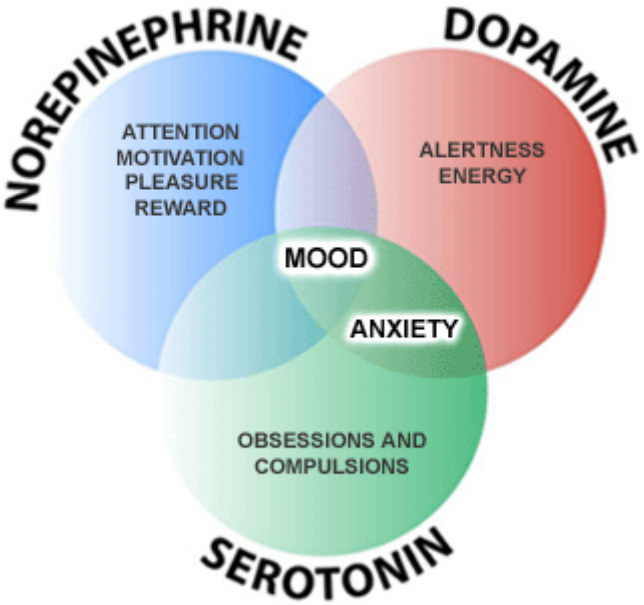

Figure 1.Neurotransmitters in the brain affecting mood[90].

That these neurotransmitters indeed play a role in OCD is supported by the effects of medication used in the treatments, such as Clomipramine and Fluvoxamine[15]. These medications have to do with inhibiting the reuptake of serotonin, which will be more extensively described in chapter 4**.** Because the precise role of the neurotransmitters remains unknown, patients with OCD often have to try several different medications[15].

With regard to the neurobiological basis of OCD, the prefrontal cortex has been consistently associated with OCD [20]. A correlation was found between severity of OCD and damage and abnormalities in the prefrontal cortex[20]. That the prefrontal cortex is important in OCD has been quite extensively studied. It can be explained with the Supervisory Attention System/Contention Scheduling System (SAS/CSS) model of 'willed and automatic control of behaviour', composed by Shallice in 1982[26,27]. In summary, the CSS system selects and sequences behavioural responses. The system eventually inhibits itself once the response is complete[20]. The SAS primes and edits the selection of the responses of the CSS, based on abstract non-physiological internal information. The CSS can be found in the basal ganglia[27], whereas the SAS lies in the Prefrontal cortex[20]. It is found that a disruption of the CSS system leads to stereotypical repetitive behaviour[28]. A disruption in the SAS system however can lead to compulsive behaviour[28,27].Indeed, brain studies on people suffering from OCD confirm this role of the prefrontal cortex [16, 20, 28]. These mechanisms are more extensively explained in chapter 4.

2.4 Genetics

There is evidence for a genetic basis for OCD, which is mostly derived from twin studies[29].Heritability for obsessions is estimated higher than for compulsion, respectively 33% and 26%[30]. However, the study of the genetics (just as for the study of the molecular mechanism) behind OCD is, as with many mental disorders, a difficult process,since most psychiatric disorders are mostly descriptively defined. It is difficult to find endophenotypes. The research for genetic basis for OCD is mostly hampered by heterogeneity and the lack of the understandings of the molecular mechanism[31].

A number of candidate genes, related to the serotonin and dopamine system, have been mentioned in the literature and selected, such as Catechol *O*-methyltransferase-low enzyme activity (COMT-L) [32], GABA-A-Ÿ2[33] and monoamine oxidase A[34]. In scheme 2, an overview is copied from the paper of Pato et al. (2002) with proposed genes involved in OCD[31]. Pato*et al.* (2002) suggests to narrow the phenotype of this disorder to create more homogeneity, to facilitate the research for "OCD genes"[31].

Candidate Genes in Obsessive-Compulsive Disorder[a]

Candidate Gene	Positive Findings	Negative Findings
5-HT_{2A}	Enoch et al,[18] 1998	Nicolini et al,[19] 1996; Pato et al,[20] 2001; Bellodi et al,[5] 2001
SLC6A4	McDougle et al,[21] 1998; Bengel et al,[22] 1999	Billett et al,[23] 1997; Ohara et al,[24] 1998
TPH		Han et al,[25] 1999; Frisch et al,[26] 2000
5-HT_{2C}		Nicolini et al,[19] 1996; Cavallini et al,[27] 1998
5-HTT	Bengel et al,[22] 1999; McDougle et al,[21] 1998	Pato et al,[20] 2001; Billett et al,[28] 1998
5-$HT_{1D\beta}$	Mundo et al,[29] 2000; Pauls,[30] 2001	Bellodi et al,[5] 2001
DRD2		Nicolini et al,[19] 1996; Billett et al,[28] 1998; Novelli et al,[31] 1994
DRD3		Nicolini et al,[19] 1996; Billett et al,[28] 1998; Catalano et al,[32] 1994
DRD4	Cruz et al,[33] 1997; Billett et al,[28] 1998	
DAT-1		Frisch et al,[26] 2000; Billett et al,[28] 1998
COMT	Karayiorgou et al,[12] 1997; Alsobrook et al,[34] 1999; Schindler et al,[14] 2000	
MAO-A	Camarena et al,[16] 2001	
MOG-2		Kennedy et al,[35] 2001
MOG-4	Kennedy et al,[35] 2001	
HLA-CAR		Kennedy et al,[35] 2001
GABA-A-γ2		Richter et al,[15] 2001

[a]Abbreviations: COMT = catechol *O*-methyltransferase, DAT-1 = dopamine transporter, HLA-CAR = human leukocyte antigen–CA repeat, MAO-A = monoamine oxidase A, MOG = myelin oligodendrocyte glycoprotein, TPH = tryptophan hydroxylase.

Scheme 2.Overview of candidate genes for OCD[31].(copy from Pato et al., 2002)

3. Autism - Human

3.1 Autistic disorder

Autistic disorder, also known as autism, is part of a group of disorders called Pervasive Developmental Disorders (PDD)[3]. These PDD's are defined by a pattern of deficits in certain behavioural patterns[35]. They are characterized by a severe impairment in skills of communication, reciprocal social skills, and stereotyped behaviour might be present also[3].

The national institute of neurological disorders and strokes defines autism as following: "Autism spectrum disorder (ASD) is a range of complex neurodevelopment disorders, characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behaviour" [36]. There are some other mental disorders related to autism, called autistic spectrum disorders. An overview of autism and these disorders can be seen in figure 2, which is a copy of a figure in the article of Lord and Risi (1998)[10].

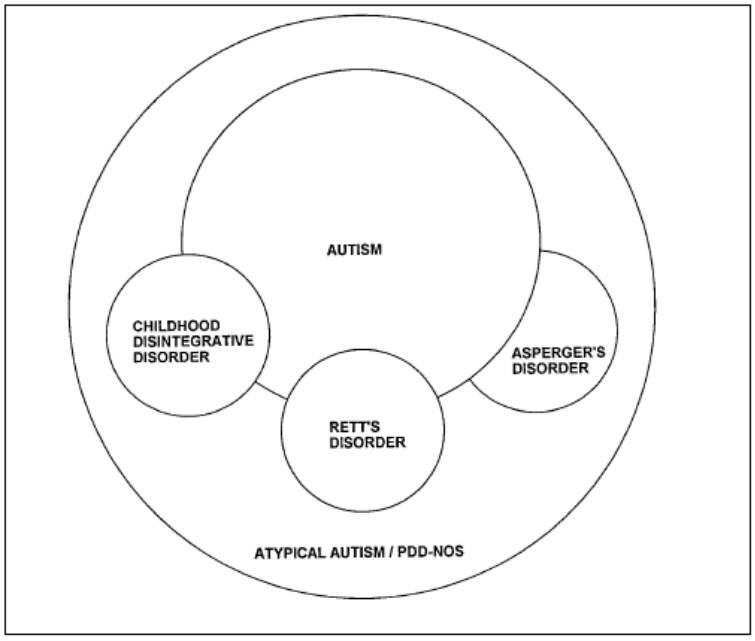

Figure 2.Autistic spectrum disorders.(Copy of Lord and Risi (1998)[10] Frameworks and methods in diagnosing autism spectrum disorders. Mental retardation and developmental disabilities research reviews 4: 90-96)

As seen in this figure, there are multiple disorders that have similar features as autism.
One category of these disorders shares the same features with autism, but is not as severe[35]. This is called atypical autism, and is also referred to as Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)[35]. There are also disorders that are similar to autism in behavioural features, but that are different in how they develop over time[35]. An example of such a similar disorder is Asperger's disorder. Children with Asperger's disorder can be distinguished from autistic children because in contrast to autistic children, they do have a "normal" development of language[35]. See scheme 3 for the DSM-IV-TR description for autism and autistic disorders[3]. The prevalence of autisticdisorder is about 5 per 10.000 individuals[3]. Distribution amongst males and females is not equal; males have a fivefold higher prevalence of autistic disorders than females[3].

Diagnostic criteria for 299.00 *Autistic Disorder*

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):
    - qualitative impairment in social interaction, as manifested by at least two of the following:
        a. marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
        b. failure to develop peer relationships appropriate to developmental level
        c. a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
        d. lack of social or emotional reciprocity
    - qualitative impairments in communication as manifested by at least one of the following:
        a. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
        b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
        c. stereotyped and repetitive use of language or idiosyncratic language
        d. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
    - restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
        a. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
        b. apparently inflexible adherence to specific, nonfunctional routines or rituals
        c. stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
        d. persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

Scheme 3.Overview DSM-IV-TR description for autistic disorders (copy from DSM-IV-TR).

3.2 Diagnostics

Autism is a disorder which becomes manifest in the first three years of life[11]. A child is diagnosed with autism if there is clear evidence of the occurrence of difficulties in each of the 3 area's A-C mentioned in scheme 3, and if there is a history of abnormalities in at least one of these areas prior to 36 months of age[35].

It is however difficult to diagnose children with autism, since many of the autistic spectrum disorders overlap with autism. Also, autism varies a lot between individuals. There is not one clear behavioural expression of this disorder. The severity varies widely: intelligence can range from superior to deficient, and language can vary from none to grammatically complex[35].
Some examples of how criteria A-C might manifest in autistic individuals are provided underneath.

Criterion A

Individuals with autism have great difficulties with reciprocal social interaction[3]. They are likely to be significantly impaired in their use of non-verbal behaviour[3]. For instance, many autistic individuals share the feature of making unusual eye contact[37]. However, this might also differ between individuals[37]. Some individuals might watch faces of other people, but not as a way of communicating[37]. Others might use gaze as a form of requesting attention[38]. Many autistic individuals have difficulties forming peer relationships; this may differ at different ages[3]. Young children might have little interest in making friends, whereas older individuals might want to establish relationships, but lack the social skills[3]. Often, individuals with autism have impaired awareness of others[3]. They often do not understand or notice other people's emotions or distress[3].

They have impairments in their communication, both verbal and non-verbally[3]. There might be a delay in speaking, or a total lack of spoken language[3]. Children that do speak often have difficulties in engaging in conversation with others[3]. They might also have a stereotyped and repetitive use of language[3]. There is also often a disturbance in the social context of language[3]. For example, autistic individuals might not understand sarcasm or irony[3].

Not only do autistic children have difficulties in social skills, they might also engage in restricted, repetitive and stereotyped behavioural patterns[3]. They often have difficulties with changes, such as furniture rearrangements[3]. Stereotyped movements may involve rocking or odd hand movements[3]. Also, they might be highly attached to inanimate objects[3].

Criterion B

Prior to the age of three, there must be abnormalities in at least one of the three criteria mentioned under criteria A[3]to diagnose a person with Autistic disorder.

Criterion C

If there is normal development, this period must not exceed past the age of three[3]. Also the disorder must not be a better fit with Rett's Disorder*(a neurodevelopmental condition where children experience an unexceptional development during the first months, and then experience a rapid degression[39]. Speech slows and they often perform repetitive hand movement.[39])*or Childhood Disintegrative Disorder*(after at least two years of normal development, children suffering from this condition show a distinctive pattern with severe developmental regression in multiple areas).*[3].

All in all, it remains quite difficult to diagnose children with autism, or disorders that fall into autistic spectrum disorders. There is still much debate on this topic. For instance, maybe the age of three should be brought up to five[35].

3.3.Working mechanism

The working mechanism behind autism has been widely studied. However, the molecular and neurobiological basis of autistic spectrum disorders still remains largely unknown[40]. Since autism is characterized by great social impairments, structures in the brain that regulate social behaviour, such as the amygdala and related structures, have been a topic of interest[11]. Figure 3 shows the location of the amygdala in the brain.

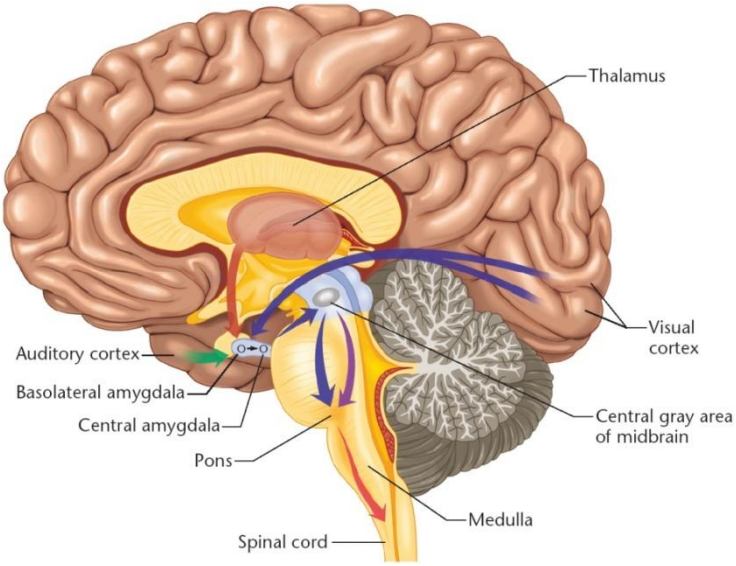

Figure 3.Overview of neural structures[41].

The amygdala is a part in the brain that consists of a collection of different nuclei[42]. The amygdala has a function in drive-related behaviour , for instance sexual behaviour, and emotions related to this[42]. Studies done with primates have shown the importance of the amygdala in social behaviour[43, 44, 45]. Rhesus macaques with lesions in the amygdala became socially isolated and failed to initiate social interactions[42]. In humans, neuroimaging showed that the amygdala is activated when signals of social importance are decoded, such as expression recognition, body movement and gaze[46, 47].
In support of involvement of the amygdale in autism, different studies found evidence for amygdala abnormalities in autism[42]. For example, Sweeten *et al.* (2002) found thatbehavioural patterns associated with damage in the amygdala (bilateral damage[48]) and temporal lobe structures related to the amygdala; resemble behaviour patterns as seen in autistic individuals[11].

However, other brain areas may also be of importance. Acosta and Pearl (2004) found alterations in total brain volume in autistic individuals[49]. These alterations were found in the cerebellum, frontal lobe and limbic system, which were all smaller in autistic subjects[49]. They found a pattern of increased rate of brain growth, followed by a decreased growth rate[49].

The cerebellum, frontal lobe and limbic system, are all brain structures that are involved in some way with emotions[49]. For further insight in these brain structures and how they may be related to autism, the article of Acosta and Pearl is recommended[49].

3.4 Genetics

The molecular and neurological mechanisms of autism still remain largely unknown, which makes the study for genes involved in autism or autistic spectrum disorders complicated. There is quite some evidence though that suggests a hereditary factor. It was found that a much larger than expected number of family's contained more than one autistic child. Also, twin studies revealed that there was a significantly higher accordance for autism in monozygotic twins than in dizygotic twins[50]. Nevertheless, it remains difficult to designate genes that might be involved in autism.

However, since the 1990's, candidate genes have been proposed and genetic loci of potential interest were identified[50]. Abrahams and Geschwind (2008) have written a review article discussing the progress made so far[50]. They state that autism has a strong genetic basis, based on existing literature[50].

Evidence is found for cytogenetic abnormalities[51]. This means that there are abnormalities in the chromosomes[51]. In a review article by Folstein and Rosen-Sheidly (2001) the authors conclude that indeed genetics seem to explain a significant proportion of the aetiology for autistic disorder[51],even though most cases still remain idiopathic. Nevertheless, some chromosomal regions of interest have been found, particularly on the chromosomes 2,7, 15 and X[51].

Wang *et al.* (2009), among others, have done a genome wide association study, and found a strong association for six single nucleotide polymorphisms (SNP's) between CDH10 and CDH9 and autism[52]. These genes code for cadherin, which is a cell-adhesion molecule[52]. They implicate a role for neuronal cell-adhesion molecules in the pathogenesis of autism[52].

For this thesis, further information on this topic is irrelevant, however, for further information on this topic the review articles of Abrahams and Geschwind (2008) and Folstein and Rosen-Sheidly (2001) are recommended.

So a small background on what OCD and autism is, and how this works in humans has now been provided. This background is necessary to try and unravel whether these disorders also exist in companion animals.
First, OCD will be discussed. To attain a good understanding of this disorder in pets, the subject will be narrowed mostly to canines and cats. This is because these companion animals have been extensively studied for this disorder and can therefore provide a good example.

4. Obsessive compulsive disorder – pets

4.1 OCD and stereotypic repetitive behaviour

As been mentioned in chapter 2, OCD in humans is defined by: "An anxiety disorder characterized by unreasonable thoughts and fears (obsessions) that lead individuals to perform repetitive behaviours (compulsions)". With reference to this definition, immediately a problem arises with diagnosing towardscertain aspects in dogs or cats:e.g.How will you be able to determine if dogs or cats have unreasonable thoughts and fears? And if so, are they so-called "obsessive"? Meaning, are they persistent and experienced as intrusive and inappropriate, causing anxiety or distress[3]?

To overcome these diagnostic complexities, it appears better to approach this problem from a different angle.A feature that is typically observed in human patients with OCD and that is also frequently observed in many animal species is stereotypic behaviour.Addressingthe topic of human obsessive compulsive behaviour as compared to animals, there are quite some similarities with stereotypic behaviour as observed in many animal species. Stereotypic behaviour in animal research is defined as *a behaviour pattern that is repetitive and invariant, and does not serve an obvious goal or function*[53].

This kind of behaviour is observed and thoroughly described in many captive animal species, e.g. zoo animals, laboratory animalsand domestic animals, especially if kept in cages, or otherwise poor environments[54,20]. Stereotypical repetitive behavioursare classified as abnormal behaviours, since thesebehaviours do not typically occur in the wild[20].

So both the defined human OCD and stereotypic behaviour in animals have in common that certain behavioural patterns are performed in *a repetitive way*. A key difference between these two defined types of behaviour seems to be that in OCD, the behaviour appears to be goal-directed, whereas in stereotypic behaviour this is supposedly not the case[20]. For example, excessive grooming in cats, which is a goal directed behaviour, compared to pacing which is seen a lot in zoo animals[20].Nevertheless, it remains difficult to come to a strict, unambiguous distinctive description of both phenomena.

However, there are some types of repetitive behaviour in animals that seem to resemble some of the obsessive compulsions observed in humans with OCD[54]. An example of this sort of behavioural patterns is excessive grooming patterns in cats or dogs, which might be comparable to the hand washing in humans: a behaviour that is functional in its original form, but that is no longer functional but rather compulsive (and obsessive in humans)in the presented pathological form. Interestingly, there is evidence for a similar underlying neurobiological mechanism: animals performing this typical abnormal repetitive behaviour respond to the same pharmacological treatment used for humans in OCD[54].

However, can we actually diagnose companion animals performing stereotypical behaviour with OCD? There is an ongoing debate on how to call this disorder in companion animals. Luescher (2003) argued that it is better to group this behaviour under compulsive disorder, leaving the *obsessivity*out of the description[54]. His argument for leaving obsessivity out is that obsessions are a typical human measure, which cannot be measured in dogs or cats, since these are based on (intrusive) thoughts[54]. This view is in line with a recent publication of Tiira et al. (2012)[9]. Therefore, it appears better to refer to this disorder as Canine Compulsive Disorder and Feline Compulsive disorder (respectively CCD and FCD).

So since the definition of OCD in humans does not apply here, what would be a better definition to describe these disorders? Dodman*et al.* (2009) formulated the following definition: "Time-consuming, repetitive behaviour causing distress and functional impairment"[55]. However, this definition could just as easily describe stereotypic behaviour, since this is also repetitive behaviour. Also, stereotypical repetitive behaviour can be a behaviour that has become independent from its original causes, and is therefore persistent, but not necessarily causing distress[56].Therefore, to

distinguish this disorder, it would be better to add the fact that compulsive disorders seem to be goal directed[20]. This would make the definition something like: "Time-consuming, repetitive goal-directed behaviour causing distress and functional impairment"[20, 55],with stereotypical repetitive behaviour not serving any goal. Nevertheless, even with the addition of goal-directed behaviour, the distinction between stereotypic repetitive behaviour and compulsive behaviour remains difficult.

Hewson and Luescher have made a working definition for diagnosing CD which is the following: *"Behaviours that are usually brought on by conflict, but that are subsequently shown outside of the original context. The behaviours might share a similar pathophysiology (e.g. changes in serotonin, dopamine and beta-endorphin systems). Compulsive behaviours seem abnormal because they are displayed out of context and are often repetitive, exaggerated or sustained"*[57].

This definition does seem more complete, but it does forget to mention that compulsive behaviour is usually first shown in context. When the behaviour starts to become more compulsive, it is also shown out of context. More on the development of compulsive behaviour can be found under the section development.

Another way to view these behaviours could be by using the termperseveration.Perseveration is the persistence of an action after the stimulus has already been ceased[20]. There are different kinds of perseveration that can be distinguished. There are levels of perseveration that describe the action as an inappropriate repetition of complex motor movements, which resembles what is usually referred to as stereotypical repetitive behaviour[20]. There are also forms of perseveration that describe the action as an inappropriate repetition of goals or rules, hence resembling more of (obsessive) compulsive behaviour[20].

These different kinds of perseveration have also been linked to different brain regions, therefore creating the possibility to make a distinction of (obsessive) compulsive behaviour and stereotypical repetitive behaviour on a neurobiological level[20]. Which brain regions have been associated with the different kinds of perseveration and a more elaborate explanation of the different forms is given under the section working mechanism.

The next section will describe repetitive behaviour in animals which can occur in a compulsive form and has been thought of to resemble OCD in humans.

4.2 Symptoms/Behaviour

There are quite some behaviours in dogs and cats which are now viewed as compulsive behaviour, or can occur as such. These behaviours can be categorized.
Among the categories of CD types as mentioned in the literature for dogs and cats are: repetitive locomotorybehaviour, repetitive oral behaviour, excessive aggression related behaviour, repetitive vocalization and hallucinatory behaviour.

Different kinds of behaviour performed by dogs and cats for each category are summarized in table 1 below. It is important to understand that the behaviour listed in this table does not necessarily always reflect compulsive behaviour. Many of the behaviours mentioned below can have multiple causes. For instance, freezing might be anxiety related[58].

Also, when a dog or cat performs a behaviour listed in the table below; this does not always have to be compulsive. A behaviour is viewed as being compulsive when it is: repetitive, exaggerated or sustains action that interferes with the animal's normal functioning, is displayed out of context (this is at a later stage) and is not due to any other medical problem.

Table 1.Behavioural categories for dogs and cats with OCD resembling behaviour in the literature [54]

Behaviour category	Dogs	Cats
Repetitive Locomotory	Circling, tail chasing, pacing, jumping in place, chasing light reflections, freezing	Circling, sudden agitation, skin rippling, ducking, freezing
Repetitive Oral behaviour	Leg or foot chewing, self-licking, air or nose licking, flank sucking, scratching, chewing/licking objects, snapping in the air, pica*	Leg or feet chewing, over grooming, chewing/licking objects, wool sucking or eating, pica*
Aggression related behaviour	Self-directed aggression, attacking food bowl/inanimate objects,	Self-directed aggression – especially towards own tail
Repetitive Vocalization	Rhythmic barking, rhythmic whining	Persistent meowing, persistent howling
Hallucinatory	Staring at shadows, chasing light reflections, startling	Staring at shadows, avoiding imaginary objects, startling

* Pica : non-food material is repetitively ingested[59].

Figures 4 and 5 are examples of dogs performing a behaviour which can be compulsive.

Figure 4.A Dalmatian performing foot chewing (Copy from Luescher, A.U.,2003[54])

Figure 5. A Great Dane which would stand under a curtain and freeze. (Copy from Luescher, A.U.,2003[54])

Even though analyzing stereotypical repetitive behaviour remains a problem, veterinarians do make diagnoses of CD's in dogs and cats. How they come to such a diagnosis shall be discussed in the next section.

4.3 Diagnosis

To diagnose dogs or cats with CCD or CFD, a detailed protocol is followed[60]. First, all possible alternative factors that could be causing the behaviour have to be ruled out[54].
This can be for example other medical problems. It could for instance be that a dog is simply experiencing pain and therefore keeps on sucking its own tail[57]. In other words,a basic medical examination is required in order to rule out any other physical medical problems.

If there does not seem to be a physical medical problem, then one may take a closer look at the behaviour of the animal. A detailed history assessment of the animal is very important. This history can be divided in three parts[57]:

- Life history and management
- Disposition and temperament of the animal
- The typical characteristics of the CD itself

Life history

The background of the animal is essential to explore: where did the animal come from and also management related issues include exercise, feeding and owner interaction should be considered.[54,57,60]This is of particular importance since CCD and CFD often reflects behaviour which has been conditioned by the owner. So how the owner reacts to the behaviour of the dog is very important to identify.

Disposition and temperament

The disposition is important, since some dog breeds are more prone to (certain) compulsive behaviours, e.g. tail chasing in Bull Terriers[66]. Since CD is likely to be genetic, it is important to know if the parents or siblings also perform(ed) a similar behavioural repertoire.A behavioural profile can be made by using a questionnaire. If there are problems with the temperament of the dog or cat, these problems should be addressed first.[60]

Diagnosing Compulsive behaviour in practice

This includes information such as: frequency and duration of the compulsive behaviour, age of the animal at onset, changes of the behaviour over time and previous attempts of the owner to treat this behaviour. It is also important to know what triggers the behaviour, and if the dog or cat can be distracted when performing this behaviour.[60]
This gives insight into the degree of perseveration.

Aforementioned topics provide an overview of information that is required to make it possible to diagnose the degrees of pathology of the behaviour of the animal and gives information to formulate the prognosis. It is important to understand that this is an outline, and most veterinarians or behaviourists will ask for more information such as a video of the behaviour and more background on the behaviour itself. For more detailed information on this diagnosing subject, the BSAVA manual of canine and feline behavioural medicine is recommended[57]. Subsequently, the diagnostic features for compulsive behaviour as stated by the BSAVA are as following[57]:

-the behaviour is often repetitive, exaggerated, or sustains action that interferes with the normal functioning

-the behaviour is displayed out of context and does not exist of a purely conditioned response

-the behaviour may subsequently also be shown outside of the original context

-the behaviour is not due to a physical lesion or another pathological process

With these guidelines, a diagnosis of a compulsive disorder can be made in domestic animals, and an appropriate treatment approach may be designed. The different kinds of treatment for CD will be discussed later, under the section ‘treatment’.

4.4 Development

In the literature it appears that most of the dogs and cats suffering from CD have abnormalities in certain brain regions, and in the function of particular neurotransmitters, which shall be discussed in the coming section. It is seen however, that the onset of CD often starts with some sort of conflict situation (eventually shown by conflict behaviour), and that this behaviour is an expression of stress, frustration or conflict[61].

For instance, when an animal is motivated to perform a particular behaviour (a male wants to go outside to find a mate), but is prevented from doing so (doors are closed), there will be a conflict[61] in actual motivation of the animal and its environmental conditions to fulfill its motivation. In chronic situations (actually still motivated to go out, but no opportunity due to the closed doors for instance), behavioural patterns actually shown to fulfill this motivation might return to ambivalent conflict behaviours (searching for the open door again and again may result in pacing) and in this way become repetitive. The actual repetitive performance of this movement will release opioids which on its turn give the animal a rewarding sensation, reinforcing the animal to repeat the pattern again, and makes the pattern self-rewarding [61].

It could also be that the compulsive behaviour is reinforced by the owner[61]. By giving the animal attention when performing conflict behaviour, the behaviour can get reinforced to the extent of becoming compulsive [61]. When this is the case, the animal will only show this compulsive behaviour in the presence of its owner[57, 61], but can be emancipated in a later stage by its aforementioned self-rewarding characteristics.

It is found from clinical cases, that many compulsive disorders in dogs (and likely cats) are breed specific[61]. This might be due to a genetic component, and indeed some breeds are more susceptible for CD than other breeds[61]. Table 2 provides an overview of breed predispositions for compulsive behaviour. The topic on genetics and CDs in companion animals is discussed later.

Table 2. Overview of common repetitive behaviour in certain breeds[57, 60]

Breed	Common repetitive behaviour
Doberman Pincher	Flank sucking
English Bull Terrier	Spinning in tight circles, tail chasing[76], sticking head under or between objects, freezing
Staffordshire Bull Terrier	Spinning in tight circles
German Shepherd Dog	Tail chasing
Australian Cattle Dog	Tail chasing
Miniature Schnauzer	Checking hind end
Border Collie	Visual fixations e.g. shadow staring
Large-breed dogs	Persisten licking(causing granulomas)
Siames/Burmese cat	Wool sucking

Apparently, some breeds appear to perform certain forms of compulsive behaviour. This can be explained through behaviouralcharacterstics they were selected for. For example, Border Collie's have been selected for herding sheep[62]. Hence, dogs of this breed are motivated to perform this sort of behaviour, due to human selection. So they are more likely to perform a compulsive behaviour which is related to this inner motivation, such as shadow staring.

4.5 Underlying neurobiological mechanism of compulsive behaviour

In humans the prefrontal cortex is involved with OCD, as well as dopaminergic and serotonergic systems. Dopaminergic drugs[63] and drugs that inhibit the reuptake of serotonin are also proven to be effective in the treatment of CD in dogs[64].
The possible brain area's involved in (O)CD in pets will be discussed below, followed by the role of neurotransmitters.

As mentioned before, there are many different forms of stereotypical behaviour, which cannot be classified as *compulsive behaviours*. In the sections 4.1 through 4.3a distinction was made on the level of behaviour. This section will focus on the distinction on the neurobiological level.

Perseveration, the persistence of an action after the stimulus has already been ceased, is a sign of a dysfunction in the brain area's corresponding with executive processing[20]. There are three distinguishable forms of perseveration[20]:

-continuous perseveration

An inappropriate repetition of individual (motor) movements[20]. For example human: writing your name over and over again when asked to write it down once[20]

-recurrent perseveration

An inappropriate repetition of more complex motor movements[20].
For example human: when asked different questions, responding to each question with the same answer as to the first question[20]

-stuck-in-set perseveration

An inappropriate repetition of goals or rules. Individual responses remain flexible however[20]. For example human: if shown a deck of cards and asked to name the suit of each card, this will be no problem[20]. If subsequently the number of the cards has to be named, the person will continue to name the suit instead of the number[20]

It is seen that in the last form of perseveration, goals are included. So this form of perseveration is of interest with regards to the understanding of compulsive behaviour.
The first two forms of perseveration have been linked with the basal ganglia[65], whereas stuck-in-set perseveration has been associated with the prefrontal cortex[66]. They found this by using human subjects with frontal lesions to perform different kinds of perseveration testing tasks[66]. So, compulsive disorders in humans appear not only behaviourally different from stereotypicalbehaviours, but appear also neurobiologically distinct, as was already discussed briefly in chapter 2.

The existence of this neurobiological difference has been shown in a study of Turner (1997)[28]. He did a study with autistic children. These children were provided with two different tasks. The two-choice gambling task and the Wisconsin card sorting task.
Each of these tasks, measures a different form of perseveration. The first measures recurrent perseveration, whereas the latter measures stuck-in-set perseveration. [28]

With the two-choice gambling task, the subject is shown two boxes on a computer screen during each trial. He has to choose one of the boxes and is told to find the rule which governs which box to choose. However, the subject does not know that there actually is no rule, and it is told on a random basis if his choices are correct (so on 50% of the trials). Subjects that do not suffer from recurrent perseveration should then make random sequences, for instance: L (eft) R(ight) R L L R, and subjects that do suffer from recurrent perseveration will produce repetitive sequences, such as: L LLL R RRR L LL. [28]

The Wisconsin card sorting task measures if subjects suffer from stuck-in-set perseveration[20]. In this task, subjects receive a deck of cards[67]. Each card can vary in color, number and shape. For

instance, you can have a card with three blue circles, or a card with two red squares. Four cards are placed in front of the subject varying among these three factors. These are the key cards. The subject is than asked to match the deck of cards with the key cards. So the subject has to choose a strategy of how to organize the cards, for example, it could be that the cards are organized on shape, so squares under squares etc. [67]

The examiner tells the subject if a card is placed right or wrong. After placing ten consecutive cards right, subsequently, the examiner changes the strategy without telling the subject. So now the subject has to adjust to a new strategy. It ends when the deck of cards is empty. The severity of perseveration is then determined by the number of mistakes and the number of categories the subject was able to achieve. [67]

Turner (1997) let the autistic subjects perform both tasks to measure their recurrent and stuck-in-set perseveration[28]. However, he found no correlation for the two types of perseveration[28]. Stuck-in-set perseveration was also not correlated with scores for stereotypy as expected, and recurrent perseveration was also not correlated with impulsive/obsessive behaviour[28]. Conclusively, the underlying mechanisms appear to be different in humans.

So far, such differences, between the role of the basal ganglia and the prefrontal cortex in stereotypical and compulsive behaviour,appear reliable in animals as well, however, no neurobiological difference between stereotypical repetitive behaviour and compulsive behaviour are found yet.

For example, the difference between stereotypical repetitive behaviour and compulsive behaviour has been tested in laboratory mice that performed an abnormal behaviour called barbering, which is similar to hair-plucking in humans (trichotillomania)[20]. Barbering is a behaviour in which one mouse plucks fur and whiskers from other mouse in its cage, or from itself[68].

They studied the relationship between stereotypy, the barbering behaviour, and recurrent and stuck-in-set perseveration[20]. They used a modified version of the two-choice gambling task to test the recurrent perseveration, and a different task to measure stuck-in-set perseveration, called the Intra Dimensional – Extra Dimensional set shifting task[20] (see for an elaborated explanation of this task, Owen *et al.*,(1993))[69]. They found that indeed stereotypy and the severity of barbering were not correlated[20]. Also, stereotypy and stuck-in-set perseveration were uncorrelated, just as the severity of barbering and recurrent perseveration[20]. So, indeed, it seems probable that compulsive behaviour and stereotypic behaviour are separate phenomena with different underlying mechanisms.

It is however quite difficult to measure these different types of perseveration in animals, since most of the tasks to measure different kinds of perseveration were designed for humans and contain many spoken directions[20]. So the tasks have to be modified to apply them on animals. So they did for mice, but it can still be questioned if differences can also be found in dogs and cats?

Very recently, a research was conducted with dogs of various breeds, to try and find if there was also a difference in stereotypic behaviour, compulsive behaviour and recurrent and stuck-in-set perseveration[70]. In this study the two-choice gambling task and an intro-dimensional extra-dimensional set shifting task were used[20]. The latter is a task that measures stuck-in-set perseveration[20]. However, no differences were observed [70];there were no correlations for the control subjects and the 'abnormal' subjects with generally perseverative behaviour[70]. Thus, in this study they found no evidence that could point to different underlying neurobiological mechanisms. The researchers do state that this might have been due to the mild expression of abnormal repetitive behaviour in the subjects[70]. Also, the tests might not have been modified well enough to test for stuck-in-set perseveration[70].

So, not much is known yet regarding the different underlying brain regions that might be important in compulsive disorders. However, it is an area that is beginning to receive attention from multiple scientists, so there is ongoing research regarding this topic, in different animal species.

As said before, the neurotransmitters serotonin and dopamine also seem to play a role in compulsive behaviour in domestic animals. So far medication that influences these neurotransmitters has proven to be effective in treating compulsive disorders in dogs and cats[57] and might give additional information on the working mechanisms behind these disorders.

It was found that drugs inhibiting serotonin reuptake, so called SSRI's (Selective Serotonin Reuptake Inhibitors), have proven to be the most effective drug in treating CD in dogs and cats[57]. Clomipramine is most often used in treating compulsive behaviour[57]. It usually takes several weeks for these drugs to show an effect[57]. This is an indication that their effect is probably due to a cascade of events which is triggered by an accumulation of serotonin, instead of serotonin accumulation in the synapse alone[71].

Dopamine antagonists can also be effective in treating CD; however these are usually not used for companion animals, since the effective doses have not been well established[57].

Some research also showed that β-endorphins might also be of importance, since some dogs performing tail-chasing behaviour responded to narcotic antagonists[72]. Also, treatment with β-endorphins antagonists has proven to be effective in temporarily suppressing compulsive behaviour[72]. So it might be that they are important in the initial stage of CD development[72].

All and all, there is quite some evidence for the importance of these three neurotransmitters, but the true working of these neurotransmitters in individuals with CD is not yet fully understood in dogs and cats as well as in humans?[57]. It is also likely that the importance of these neurotransmitters varies with the different CD behaviours[57]. Vermeire*et al.*(2012) found in their study that in dogs affected with CD, had a lower 5-HT2A (serotonin) receptor availability in the frontal and temporal cortices[65]. Also, 78 percent of dog with CD had abnormal dopamine receptors[73], although the levels of dopamine receptorscould be either increased or decreased[73]. This study confirms the idea of the role of serotonergic and dopaminergic systems in CD. These findings are of particular interest because they indicate correspondence to the pathophysiology of OCD in humans, and therefore provide good construct validity that supports the use of canines as a natural model for OCD[73].

4.6 Genetics

Very recently, a candidate gene for canine compulsive disorder has been identified[55]. This gene has been found in Doberman Pinchers that often perform a compulsive behaviour called flank-sucking[55]. The candidate gene that was identifiedis the Cadherin 2(CDH2) gene, which is found in the chromosome 7 locus[55]. Dodman*et al.* (2010) found that dogs suffering from multiple compulsive behaviours, had a higher frequency of the risk allele for CDH2 than dogs with a less severe phenotype,, respectively 60% and 43%[55]. Unaffected dogs only had an occurrence of 22%[55]. CDH2 is widely expressed and mediates synaptic activity-regulated neuronal adhesion[55]. This is thus far the first genetic locus identified for any animal compulsive disorder[55]. Interestingly, this CDH2 gene has also been associated with human autism[9,52]. Autistic individuals also often show repetitive behaviour. This will be further discussed in chapter 5.

4.7 Treatment

So far the background of CD in companion animals and the possible underlying mechanisms of CD in companion animals have been described. So how can we use this information to treat pets with this disorder?

The three main components of present CD treatment consist of changing the environment and the social interactions of the animal, modification of the behaviour and pharmacological treatment[57].

If the animal is harming itself, this has to be prevented, for instance using a muzzle. There should not be interactive punishment for the behaviour (this can increase stress and reinforce the behaviour)[57]. Also, daily exercise and enrichment should be increased[57].

The first component has to do with changing the environment. The behaviour is often related to stress, and the triggers for this behaviour should be removed if possible[57]. If this is not possible, the animal has to be desensitized to this trigger[57]. Stress in the environment can be reduced by avoiding inconsistent interactions, and providing regular routines to the animal [57]. It is important for an animal to have a certain level of control over its environment[74].

Secondly, animals may be motivated to perform alternative behavioursby the use of behavioural therapy[57]. One may distract the animal when it is initiating the compulsive behaviour[57]. Subsequently, one may give a command for a behaviour that is incompatible with the compulsive behaviour and reward the animal for performing this other behaviour[57]. This might sound easier to achieve for dogs, but cats are also able to learn commands[57]. If they are not trained, cats might be distracted by providing a toy[57].

Thirdly, most animals suffering from CD receive pharmacological treatment to treat severe forms, or to facilitate the behavioural interventiontreatment[57]. As mentioned before, most drugs have to do with serotonin[57]. SSRI's are often used (selective serotonin reuptake inhibitors like fluoxetine, paroxetine, sertraline)[57]; as well as Tricyclic Antidepressants (TCAs), like clomipramine[57]. The problem however is that the underlying mechanism is not yet fully understood, so which drug is most effective (in which case) is not yet known[57].

After having reached a satisfactory resolution, the medication should continue for at least one more month, where after the animal needs to be gradually weaned off to prevent a rebound effect[57].

Even though there is a treatment for CD in dogs and cats, this is not as simple as it may sound[75]. Treating CD takes a lot of time and asks for consistency of the owner[75].

The prognosis for CD in dogs and cats is relatively good. In the Ontario Veterinary College, 67 % of the owners were satisfied after treatment[57]. It is however important to treat CD as soon as possible, since analysis revealed that outcome of the treatment was negatively affected by the duration of the problem[57].

OCD has now been elaborately described and discussed. From the behavioural characteristic via working mechanism to the genetics. There is quite some evidence for this disorder to be also present in companion animals, such as dogs and cats.

However, as mentioned in the first chapter, this cannot be said for all human mental disorders. A disorder that is very recently receiving some attention is autism.
The following chapter will discuss the possible occurrence of autism in companion animals, with the focus being mostly on dogs. This is because most of the research regarding this topic was based on dogs.

5. Autism – pets

5.1 Autism

Autism is a very complex disorder, which is mostly defined descriptively. The underlying mechanisms are not well known, and diagnosis is based mostly on behaviour.
In humans, this disorder can be defined as :"a range of complex neurodevelopment disorders, characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behaviour" [36].
This is of course not a definition which can easily be used for companion animals such as dogs or cats. It is of course possible to assess sociability and to observe (stereotyped repetitive) behaviour, the difficulty lies in interpreting these assessments and to identify the underlying causes.
This will be discussed below and in the coming sections.

A very important common feature of people with autism is their social impairment. This is a complex phenomenon to study in pets. When can you say that a dog is socially impaired? Such a feature might be difficult to measure, but since dogs are social animals, it might be possible to measure their 'social skills' to a certain extent.

Another problem that arises with this definition is the latter part. The restricted, repetitive and stereotyped patterns of behaviour. The problem with stereotypic behaviour has already been discussed in the previous chapter. There it was explained that there is a difference between compulsive behaviour and stereotypic behaviour. Stereotypic behaviour was defined as a behavioural pattern that is repetitive and invariant, and does not serve an obvious goal or function[53].

However, many captive animals perform stereotypic behaviour, and it is not very likely that these animals are all suffering from autistic disorders. It is however an easier topic to study, than social impairment. Especially when thinking of other, less social companion animals than dogs.

So, to study the possibility of natural animal models for human autism in pets, one could look at stereotypic behaviour, and 'autistic –like' social behaviour. These topics shall be discussed in more detail in the coming sections. It shall not be possible to follow the same structure as in the OCD section, since autism in pets is a very new area of research, and the existence of this disorder in pets is still highly debatable and is currently not a disorder that is diagnosed by veterinarians.

5.2 Symptoms/behaviour

How can one measure social impairment in dogs? Tiira*et al.* (2012) state that relevant estimates of canine social behaviour are amicability or sociability towards humans or other dogs, and aggressiveness towards other dogs[9].Indeed, some dog owners describe their dogs as being asocial, and withdrawn[76]. This is indeed behaviour that resembles behaviour seen in autistic people. However, there might just be other explanations for a dog to behave in an "asocial" way or to be withdrawn, like e.g. the level of socialization during its early life with a higher risk for fearful behaviour for unknown stimuli and being afraid or asocial towards strangers or other dogs[57].

If the dog appears to be asocial towards its owner from the very early beginning, that might be a better indication. Since, normally, a dog should be socialized at least with its own owner. Autism is a developmental disorder, and is characterized by an early onset. So the antisocial behaviour should be present since a very early age. This might help to exclude other causes for the autistic-like behaviour, such as traumatizing experiences or medical conditions. Also, autism seems to have a strong genetic base, so it would be expected that some of the siblings also show a similar behaviour. It remains difficult however to label a dog as socially impaired, in a way that is resembling autism, since many other factors might be involved. Face validity is therefore quite low.

The other component is restricted, repetitive, stereotypic behaviour. This is as we have seen in CD,abehaviour resembling stereotypies. That stereotypic behaviour is more difficult to assess than it might seem has already been revealed tackled in the chapter of OCD. In autistic humans, a co-occurrence of lower and higher order repetitive behaviours is often seen[77]. The former resembles a repetition of motor movements, whereas the latter has more to do with resistance to change[77]. Autistic stereotypic behaviour of a lower order is often not goal related behaviour, i.e. hand flapping and rocking, so they should share more similarities with the mechanisms of stereotypical behaviour than with the so defined compulsive behaviour[20]. However, the higher order repetitive behaviours in autisms, such as insistence on sameness, rituals and circumscribed interests, do have a cognitive component, and may therefore be slightly similar to the working mechanism of compulsive behaviour. This complicates the assessment of this component, since different brain areas might be involved in these two different repetitive behaviours.

On a behavioural level, this is quite hard to subdivide, but there might be a neurobiological mechanism which could provide a clearer distinction. One study in parrots for the underlying neurobiological mechanism for these stereotypies is found available[78], and will be discussed under the section *working mechanism*.

The actual start of studying the possibilities of autism in dogs, originates from the studies on stereotypic behaviour. Dodman studied compulsive behaviour in bull terriers, when he noticed that many of the owners of these dogs also mentioned their dogs were asocial and withdrawn[76]. He started to notice more behaviour which resembled behaviour seen in autistic people in Bull Terriers. This was the start of a number of studies regarding autism in Bull Terriers.

Bull Terriers are dogs from a breed that are prone to perform tail-chasing[75],abehaviour which is mostly described as a compulsive behaviour, or due to partial seizures[79,80].
However, when studying this behaviour, Dodman*et al.* came across some interesting findings. They found that males were at greater risk for developing tail-chasing than females. Also, they found a correlation of tail-chasing with episodic aggression (episodic, abnormal and uncontrollable aggressive behaviour in the absence of a significant provocationtowards humans, animals or other objects[81,9]) and trance-like behaviour[79] (behaviour where the dog seems to be in some sort of trance, and is very hard to be distracted[9)]. Interestingly, these findings are all very similar to behaviour that is seen in autistic people[79]: autism is a disorder which is more common in males than females, and is additionally associated with episodic aggressiveness, trance-like staring and repetitive movements[82].

Another interesting fact is that in dogs there is a co-morbidity with various phobias and tail-chasing[82]. Over ten percent of autistic children have noise phobias and anxiety related disorders[82]. So it might be that tail chasing is actually more closely related to autism, than to OCD. To test this, Tiira *et al.* (2012) tried to combine data of tail chasing with social behaviour[9] and assessed the relation between the level of social impairment and stereotypical behaviour. She did this by collecting behavioural data of Finnish Bull Terriers, German Shepherds and Staffordshire Bull Terriers, as well as collecting data through questionnaires regarding the dogs' social behaviour[9]. However, they could not find any relation between tail-chasing and impaired social behaviour, which was measured by aggression towards dogs or humans, and their sociability towards humans and dogs[9].

5.3 Working mechanism

Little is known about the neurobiological mechanism behind autism in humans, so this complicates the research for the working mechanism in companion animals. Currently there is no animal model for autism. The research in animals that is done on this topic has focused mainly on the stereotypic component, with the focus being on equivalents of the lower order repetitive movements. This is because these are easier to study, and have a high occurrence in most autistic people[78].

As mentioned in chapter 4three forms of perseveration were discussed addressing OCDs. Most autistic people suffer from recurrent perseveration, which can be measured through the gambling task. In a study of Garner *et al.* (2003), Orange-Wing Amazon Parrots[78] received a modified version of the gambling task. Interestingly, results showed that a high degree of stereotypy was correlated with high perseveration levels in the gambling task. The researchers suggest that these results indicate on a general disinhibition of response selection in the motor system, so in the basal ganglia. Back to humans, it is well known that autistic people with stereotypic behaviour also perform poorly in this gambling task[28] and this might be evidence for possible similar underlying working mechanisms[78].

Lewis *et al.* 2007 reviewed animal models of restricted repetitive behaviour in autism and also suggest that the basal ganglia plays an important role in the stereotypic behaviour seen in autism[77]. They say that spontaneous and persistent repetitive behaviour is associated with a dysfunction in neural circuits that are responsible for transmitting information between the cortex and the basal ganglia[77]. This is supported by several studies [83,84,85].MRI studies on autism have linked reduced caudate volume to repetitive behaviour[77]. So it is likely for the basal ganglia to indeed play a role in autism, however, there have not been any studies in companion animals so far to study this or other brain regions that might be involved.

5.4 Genetics

Autism is thought to have a strong genetic base. However, not many genes involved in autism have been identified. A gene which has been associated with autism, is the Cadherin 2 (CDH2) gene, which codes for cadherin[9]. In Doberman Pincher's, the same gene was found to be associated with the compulsive behaviour flank-sucking[55]. However, no correlation of relation of this gene and tail chasing in Bull Terriers was found in the study of Tiira*et al.* (2012)[9]. So far, no other studies for candidate genes for autism in companion animals were found available.

6. Discussion

The aim of this thesis was to reflect the current knowledge of some human mental disorders on possible similar disorders in pets. With the leading research question:
'Can we learn from human mental disorders to diagnose mental disorders in pets?'
It was hypothesized that considering similar brain structures and functioning some mental disorders, resembling the human mental disorder, should be present in pets as well, not only behaviourally, but also neurobiologically. To answer this question, two human mental disorders were used as examples, being OCD and Autism: one disorder with increasing evidence for the existence in pets as well and another disorder that is currently not described in pets.

Based on the literature as summarized and discussed in this thesis, there is sufficient evidence for the conclusion that the occurrence of an equivalent of OCD in companion animals exists. Comparable disorders in pets resemble to the human disorder on at least a behavioural level[86], and there is some neurobiological and pharmacological evidence to also support resemblance with human OCD on a neurobiological level. On the contrary, Autism in companion animals is a very new area of research: the evidence to support the prevalence of this disorder (Moon-Fanelli*et al.* (2011)[82],Tiira*et al.*(2012)[9] in companion animals is not (yet) convincing enough and too lean so far.

The two disorders will be discussed and reflected on the hand of the specifications of the levels of validity, starting with face validity, secondly predictive validity and finally construct validity.

Face validity

Face validity can be seen as the *behavioural similarity* of the disorder as it occurs in companion animals compared to humans[14]**.** This validity is considered high for OCD based on the literature of inter alia Luescher (2003)[54] and Overall (2002)[60], but still low for autism addressing the literature of Dodman*et al.*(2010)[12] and Tiira*et al.*(2012)[9].

OCD in companion animals is better referred to as CD, since the obsessive part is hard to proof due to the fact that one cannot test if companion animals suffer from intrusive thoughts or fears[54]. On the other hand, it can be seen that the compulsive part of this behaviour is very similar to compulsive behaviour patterns in humans[9]. The typical behaviour which (seems to be/) is goal directed, exaggerated, interferes with the animal's normal functioning and is not due to any medical problem[57]. This is an almost comparable description that the DSM-IV-TR has of OCD[3].

For autism, there are reports of behavioural similarities between humans and pets, but these are quite scarce and scientifically not very well substantiated[12]. Most of these concerned dogs performing either a stereotypic repetitive behaviour or a compulsive behaviour, and also seem to be entitled as *withdrawn* and *asocial*[12]. This resembles behaviour which is characteristic of autism, however, current available research has not yet been able to link these two components. No significant correlations have been found yet between stereotypic repetitive behaviour and asocial behaviour.[9].There are also too many other underlying factors that might be in play here to rule out other possible causes, think of bad socialization etcetera.

Predictive validity

The predictive validity for CD as an animal model for OCD is considered quite high[9].
When diagnosing dogs or cats with CD, this is very likely to indeed resemble the human mental disorder OCD. The diagnostic features are 'designed' to rule out other medical problems, and to distinguish CD from stereotypic repetitive behaviour. That the diagnosis is often correct, is supported by a good response on treatment with medication which is also used to treat OCD in humans(SSRI's and TCA's).

For autism, predictive validity is not yet really at issue, since the prevalence of it in animals is still a very debatable topic.

Construct validity

Construct validity is the highest scaling of validity supposing evidence of similar neurobiological mechanisms. The construct validity of dog CD for human OCD appears to be good as well.

Many dogs and cats performing compulsive behaviour respond to the same pharmacological treatment as humans with OCD, which are mostly SSRI's (selective serotonin re-uptake inhibitors)[54,57]. It is however still not fully understood how neurotransmitters are involved in CD/OCD in both humans and companion animals, so there is still not a very well designed pharmacological treatment. A better understanding of this mechanism in the future might lead to a more effective treatment for both humans and companion animals.

There is also evidence for the same underlying neurobiological mechanism in dogs and humans. The difficulty however is the difference between stereotypic repetitive behaviour and compulsive behaviour. In humans, this distinction is quite clear, and the diagnosis for OCD in humans specifically excludes stereotypy[78]. This has to do with the two different brain regions involved with these two behaviours[78]: stereotypic repetitive behaviour is associated with the basal ganglia whereas OCD has been associated with the prefrontal cortex[20, 70].

A comparable distinction in animals has been found in a study with mice as well. In dogs, such a distinction could not yet be found[70].This may be found in future research, and is likely to exist as typically pharmacological treatment does not always seem to work in all repetitive behaviour, such as over-grooming. It might be necessary for tests measuring differences between recurrent and stuck-in-set perseveration to be further and better modified to be applied on dogs and other companion animals.

To my knowing, there have not yet been studies for a similar neurobiological mechanism for autism in companion animals. The neurobiological mechanism for autism is still not fully understood in humans[40], making it quite hard to study this in companion animals. Also, as mentioned earlier, this area of research is very new and so still at the face validity stage.
Very recently, however, a specific gene was identified in Doberman Pinscher's suffering from CD, which is associated with autism in humans[55, 52]. Further research is necessary to figure out if this gene is also present in individuals? with "autistic-like" characteristics[55].

Difficulties

One of the greatest difficulties with assessing mental disorders in pets with the use of human mental disorders is that the diagnostics of these disorders often involve cognitive components. Many of these disorders are diagnosed based on behaviour and are evaluated by asking the subject questions. This is of course not feasible with (companion) animals.

So as can be seen in the examples given in this thesis, this quite complicates the matter in diagnosis. Even with disorders that have been widely studied in different kinds of companion animals, and are quite well understood, such as OCD, this is still a difficulty. For instance, how can we study if dogs performing compulsive behaviour might not also experience some sort of obsessive part?

Overall and Dunham (2002) made an interesting suggestion regarding this topic[60]. They suggest that there might be evidence for the existence of obsessionin dogs[60]. To them, it appears that dogs performing compulsive behaviour might actually perceive that this behaviour is abnormal and try to control this behaviour in the presence of others[60:] there have been reports of dogs removing themselves from view to perform these behaviours[60]. On the other hand, learning components can be considered as well for the withdrawing behaviour as the owner may always interrupt or may even punish these (self-rewarding) patterns. They did find evidence in their study for this pattern (the pet hiding from its owner to perform the behaviour) to actually exist[60]. They conclude, based on the focus their subjects had on performing the compulsive behaviour, avoidance

of interfering subjects, and being avoided by clinically healthy subjects, that a cognitive component in (O)CD is present, albeit hard to assess[60].

So, by observing and trying to modify the diagnostic features for human mental disorders for animals, one might be able to find these sorts of cognitive components as well.
However, in more complex mental disorders of which the working mechanisms remain largely unknown yet, this might not be possible in the nearby future. For example, take a disorder in which hallucinations are involved, such as schizophrenia. How would one study if a dog or a cat is hallucinating? There might be some assumed hallucinatory behaviours seen in dogs and cats, such as shadow staring and imaginary fly snapping, but proving that these individuals are actually hallucinating just in the way as humans hallucinate, will be very difficult with the current scientific knowledge and techniques[87].

Improving knowledge and techniques will enable us to reflect different on symptoms. Even if certain behaviour seems to be very similar to a mental disorder in humans, precaution is necessary, as will be illustrated by the next example.

In 1966, Fox published an article titled: 'A syndrome in the dog resembling human infantile autism[87]. In this paper dogs are described as performing autistic-like behaviours[87]. The subjects were all dogs which had been reared socially isolated (up to 16 to 32 weeks) [87]. These dogs performed stereotypic behaviour such as whirling, pacing and taking strange postures, and were also very fearful of novel stimuli[87]. They appeared withdrawn and did not respond properly to pain stimuli[87]. Treating these dogs at a later stage was almost impossible[87]. This does indeed resemble autism in humans on a behavioural level at the first sight,however, this sort of behaviour has been assigned now to the well-known phenomenon of the Kennel-Syndrome[88]: also known as socialization deficiency syndrome.

A syndrome that develops after inadequate socialization and isolation at a young age (until 4-6 months) exhibiting a very poor social adaptability at a later stage in their life[88]. Characteristics of this syndrome are: an extreme and persistent fear and timidity towards novel stimuli[88]. These dogs tend to avoid humans and it is very hard to train these dogs at a later age stadium[88].

So, even though the dogs in the study of Fox appeared to be autistic-like, they were probably suffering from a socialization deficiency. This illustrates anyhow the difficulties with identifying complex mental disorders in pets, which might resemble a human mental disorder, but are in fact due to other underlying factors.

To conclude, even though some mental disorders might be present in companion animals, such as dogs or cats, diagnosing these disorders remains a problem. This is mostly due to the complexity of these disorders, the lack of fully understanding how these disorders work, and the lack of good diagnostic handles or frameworks for diagnosing them in companion animals.

6.1 Future recommendations

Research for the prevalence of human mental disorders in companion animals, and how they might serve as natural models to better understand the working of some of these disorders is currently receiving more and more attention. There are still many difficulties to overcome however. Future research could focus more on the understandings of the working mechanism of certain disorders, to provide more clarity and back up for the existence of these disorders in pets. A better understanding of these disorders might result to better diagnostic handles techniques, paving the way for more effective treatments for humans as well as pets.

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7. References

1) McKinney, W. H. F. (1987) Animal models in Psychiatry. *Perspectives in biology and medicine. Vol. 17, 529 – 541.*

2)Stein, D. J., Dodman, N. H. , Borchelt, P., Hollander, E. (1994) Behavioural Disorders in Veterinary Practice: Relevance to Psychiatry. *Comprehensive psychiatry, Vol. 35, No. 4 pp 275 – 285.*

3)American Psychiatric Foundation. 1994. Diagnostic and Statistical Manual of Mental Disorders. DSM-IV TR

4) John M. Oldham (2005). "Personality Disorders". *FOCUS* 3: 372–382.

5)Pincus, H.A., Zarin, D.A., First, M. (1998) Clinical significance and DSM- IV. *Arch. Gen. Psychiatry.Vol. 55.Dec.1998.*

6)Kendell, R., Jablensky, A. (2003). Distinguishing Between the Validity and Utility of Psychiatric Diagnoses.*Am J Psychiatry 2003; 160:4–12*

7) Baker, T.L., Foutz, A.S., McNerney, V., Mitles, M.M., Dement, W.C. (1982) Canine Model of Narcolepsy: Genetic and Developmental Determinants. *Experimental Neurology 75. 729-742*

8) Knecht C.D., Oliver, J.E., Redding, R., Selcer, R., Johnson, G. (1973) Narcolepsy in a dog and a cat. J am Vet Med Assoc, 162; 1052-1053

9)Tiira, K., Hakosalo, O., Kareinen, L., Thomas, A., Hielm-Björkman, A., Escriou, C., Arnold, P., Lohi, H. (2012) Environmental effects on compulsive tail chasing in dogs. Plosone, Vol. 7.

10) Maynard, T.M., Sikich, L., Lieberman, J.A., LaMantia, A.S. (2001). Neural Development, Cell-Cell Signaling, and the "Two-Hit" Hypothesis of Schizophrenia.*Schizophrenia Bulletin, Vol. 27 No.3*

11) Sweeten, T.L., Posey, D.J., Shekhar, A., McDougle, C.J. (2001) The amygdala and related structures in the pathophysiology of autism.

12) Dodman, N.H. (2010) Can dogs behaving badly be a new way to treat OCD? *Science.Vol. 329.*

13) Robbins TW, Sahakian BJ (1979) ''Paradoxical'' effects of psychomotor stimulant drugs in hyperactive children from the standpoint of behavioural pharmacology. *Neuropharmacology 18:931–950*

14) Tordjman, S., Drapier, D., Bonnot, O., Graignic, R., Fortes, S., Cohen, D., Millet, B., Laurent,C., Roubertoux, P.L. 2006. Animal models relevant to schizophrenia and autism: validity and limitations. *Behav Genet DOI 10.1007/s10519-006-9120-5*

15) Mayo Foundation for Medical Education and Research. (2012) *http://www.mayoclinic.com/health/obsessive-compulsive-disorder/DS00189*

16)Aouizerate, B., Guehl, D., Cuny, E., Rougier, A., Bioulac, B., Tignol, J., Burbaud, P. (2004).Pathophysiology of obsessive-compulsive disorder.A necessary link between phenomenology, neuropsychology, imagery and physiology.*Progress in Neurobiology 72. 195-221*

17) Flament, M.F., Whitaker, A., Rapoport, J.L., Davies, M., Berg, C.Z., Kalikow, K., Sceery, W., Shaffer, D., 1988. Obsessive compulsive disorder in adolescence: an epidemiological study. *J.Am. Acad. Child Adolesc. Psychiatry 27, 764–771.*

18) Karno, M., Golding, J.M., Sorenson, S.B., Burnam, M.A., 1988. The epidemiology of obsessive–compulsive disorder in five US communities.*Arch. Gen. Psychiatry 45, 1094–1099.*

19a45)Mason, G. Rushen.J. 2006. Stereotypic animal behaviour. Fundamentals and implications to welfare.2nd edition.pp. 10.

2055)Garner. J.P. 2006.Perseveration and stereotypy-systems-level insights from clinical psychology.*Stereotypic Animal Behaviour:Fundamentals and Applications to Welfare, 2nd edn (eds G. Mason and J. Rushen)pp.121-152.*

21)Mecilexicon international. 2012. http://www.medicalnewstoday.com/articles/232248.php

22)Insel.T.R., Murphy, D.L. 1981. The psychopharmalogical treatment of obsessive compulsive disorder: a review. *Journal of clinical psychopharmacology. 0271-0749/81/0105-0304*

23)Stern, R.S., Marks, M., Mawson, D., Luscombe, D.K. 1980. Clomipramine and exposure for compulsive rituals: II. Plasma levels, side effects and outcome. *BJP 1980, 136:161-166.*

24)Psychology Today. 1981-2012. http://www.psychologytoday.com/basics/dopamine

25)McDougle, C.J., Goodman, W.K., Price, L.H. 1994. Dopamine antagonists in tic-related and psychotic spectrum obsessive compulsive disorder.*Journal of clinical psychiatry, Vol. 55.(3, suppl.)24-31.*
26) Shallice, T. (1982) Specific impairments of planning. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 298, 199–209.* In: Mason, G. Rushen.J. 2006. Stereotypic animal behaviour. Fundamentals and implications to welfare.2nd edition. pp. 125-130
27)Norman, D.A. and Shallice, T. (1986) Attention to action: willed and automatic control of behaviour. In: Davidson, R.J., Schwartz, G.E. and Shapiro, D. (eds) Consciousness and Self-regulation: Advances in Research and Theory, *Vol. 4. Plenum Press, New York, pp. 1–18.*
28) Turner, M. 1997. Towards an executive dysfunction account of repetitive behaviour in autism. In: *Stereotypic animal behaviour : Fundamentals and applications to welfare, 2nd edn. (edsG.Mason and J. Rushen)*
29) Billiet et al. in Aouizerate, B., Guehl, D., Cuny, E., Rougier, A., Bioulac, B., Tignol, J., Burbaud, P. (2004).Pathophysiology of obsessive-compulsive disorder.A necessary link between phenomenology, neuropsychology, imagery and physiology.*Progress in Neurobiology 72. 195-221*
30) Jonnal, A.H., Gardner, C.O., Prescott, C.A., Kendler, K.S., 2000. Obsessive and compulsive symptoms in a general population sample of female twins. *Am. J. Med. Genet. 96, 791–796.*
31)Pato, M.T., Pato,C.N., Pauls, D.L. 2002. Recent findings in genetics of OCD.*J.Clin. Psychiatry.2002.63. (Suppl. 6)*
32)Karayiorgou, M., Sobin, C., Blundell, M.L., Galke, B.L., Malinova, L., Goldberg, P.,Ott, J., Gogos, J.A. 1999. Family based association studies support a sexually dimorphic effect of COMT and MAO-A on genetic susceptibility to obsessive-compulsive disorder. *Biol. Psychiatry 1999;45: 1178-1189*
33)Schindler, K.M., Richter, M.A., Kennedy, J.L., Pato, M.T., Pato, C.N. 2000. Association between homozygosity at the COMT gene locus and obsessive compulsive disorder.*Am J Med. Genet. 2000; 96: 721-724*
34)Richter, M.A., Mundo, E., Sam, F. *et al.* 2001. The GABA-A-γ2 receptor gene in OCD and social phobia.*Presented at the 5th internation obsessive compulsive disorder conference;March 29-April 1. Sardinia, Italy.*
35) Lord, C. Risi, S. 1998. Frameworks and methods in diagnosing autism spectrum disorders. *Mental retardation and developmental disabilities research reviews 4: 90-96*
36)National institute of neurological disorders and stroke.2012. http://www.ninds.nih.gov/disorders/autism/detail_autism.htm
37) Dawson, G., Hill, D., Spencer, A., Galpert, L., Watson, L. 1990. Affective changes between young autistic children and their mothers. *Journal of Abnormal Child Psychology, Vol. 18, No. 3, 1990, pp. 335-345*
38)Mundy, P., Sigman, M., Ungerer, J., Sherman, T. 1986. Defining the social deficits of autism: The contribution of non-verbal communication measures.*J. Child. Psychiat. Vol. 27. No.5. pp.657-669*
39)Einspieler, C., Kerr, A.M., Prechtl, F.R. 2005. Is the early development of girls with Rett Disorder really normal? *Pediatric research, Vol. 57, No. 5, 2005*
40)McDougle, C.J., Erickson, C.A., Stigler, K.A., Posey, D.J. 2005. Neurochemistry in the pathophysiology of autism.*J. Clin. Psychiatry, 2005. 66 (suppl.10)9-18*
41) http://northofneutral.wordpress.com/2009/11/12/beware-of-amygdala-hijacks/
42) Baron-Cohen, S., Ring, H.A., Bullmore, E.T., Wheelwright, S., Ashwin, C., Williams, S.C.R. 2000. The amygdala theory of autism.*Neuroscience and Biobehavioural Reviews 24 (2000) 355–364*
43) Kling A, Brothers L. The amygdala and social behaviour.AggletonJ, editor.Neurobiological aspects of emotion, memory, and mental dysfunction. New York: Wiley, 1992
44) Emery, N.J., Capitanio, J.P., Mason, W.A., Machado, C.J., Mendoza, S.P., Amaral, D.G. 2001. The effects of bilaterial lesions of the amygdala on dyadic social interactions in rhesus monkeys (*Macacamulatta) Behavioural Neuroscience 2001, Vol. 1 1 5 , No. 3, 515-544*
45) Kling A, Steklis HD. A neural substrate for affiliativebehaviour in nonhuman primates.*Brain, Behaviour and Evolution 1976;13:216–38.*

46) Baron-Cohen S, Ring H, Wheelwright S, Bullmore E, Brammer M,Simmons A, Williams S.1999. Social intelligence in the normal and autisticbrain: an fMRI study. *European Journal of Neuroscience1999;11:1891–8.*
47) Kawashima R, Sugiura M, Kato T, Nakamura A, Hatano K, Ito K, Fukuda H, Kojima S, Nakamura K. 1999. The human amygdala plays an important role in gaze monitoring. *Brain 1999;122:779–83.*
48) Adolphs, R., Tranel, D., Damasio, H., Damasio, A. 1994. Impaired recognition of emotion in facial expression following bilateral damage to the human amygdala.*Nature 372, 669 - 672*
49) Acosta, M.T., Pearl, P.L. 2004. Imaging data in autism.From structure to malfunction.*SeminPediatrNeurol 11:205-213*
50)Abrahams, B.S., Geschwind, D.H. 2008. Advances in autism genetics: on the threshold of a new neurobiology.*Nature, Vol. 9. May 2008. 341- 356*
51) Folstein, S.E., Rosen-Sheidley, B. 2001. Genetics of autism: complex aetiology for a heterogeneous disorder. *Nature. Vol. 2. December 2001. pp 943-955.*
52)Wang, K., Zhang, H., Ma, D., Bucan, M., Glessnen, J.T. *et al.* 2009. Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature, vol. 459.*
53)Wildlife New Zealand, 2007. http://www.wildlife.org.nz/zoocheck/zoochotic.htm
54)Luescher, A.U. 2003. Diagnosis and management of compulsive disorders in dogs and cats.Vet.Clin.Small. Anim. 33 92003) 253-267
55)Dodman, N.H., Karlsson, E.K., Moon-Fanelli, A., Galdzicka,M., Perloski, M., Shuster, L., Lindblad-Toh, K., Ginns, E.I. 2009. A canine chromosome 7 locus confers compulsive disorder scusceptibility. *Molecular psychiatry (2010) 15, 8-10*
56) Cooper, J.J., mason, G.J. 1998. The identification of abnormal behaviour and behavioural problems in stabled horses and their relationship to horse welfare: a comparative review.*Equine clinical behaviour. Equine vet.J.,Suppl 27 5-9*
57) Horwitz, D.F., Mills, D.S. 2009. BSAVA manuel of canine and feline behavioural medicine. Second edition. 236-244
58) Murphiree, O.D. 1972. Reduction of anxiety in genetically timid dogs drug-induced schizokinesis and autokinesis. *Integrative Physiological and Behavioural Science, Vol.7 Nr.3*
59)PubMed Health, 2012. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002505/
60)Overall, K.L., Dunham, A.E. 2002. Clinical features and outcome in dogs and cats with obsessive-compulsive disorder : 126 cases (1989-2000). *JAMA vol.221. No.10*
61)Luescher, A., 2000. Compulsive behaviour in companion animals. *Recent Advances in Companion Animal Behaviour Problems, Houpt K.A. (Ed.). International Veterinary Information Service, Ithaca NY*
62) American Kennel Club. 2004. *http://www.akc.org/breeds/border_collie/index.cfm*
63)Kennes, D., Odberg, F.O., Bouquet, Y., DeRycke, P.H. 1988. Changes in naloxone and haloperidol effects during the development of captivity induced stereotypy in bank voles. *Journal of pharmacology 153, 19-24*
64) Dodman, N.H. Shuster, L., Court, M.H., Parker, D., Dixon ,R. 1988. Use of narcotic antagonists to modify stereotypic self-licking, self-chewing and scratching behaviour in dogs.*Journal of the American veterinary medical association. 193, 815-819*
65) Sandson, J. and Albert, M.L. (1984) Varieties of perseveration. *Neuropsychologia 22, 715–732.*
66) Luria, A.R. 1965. Two kinds of motor perseveration in massive injury of the frontal lobes. *Brain 88, 1–11.*
67) Ozonoff, S., Pennington, B.F. and Rogers,S.J. 1991. Executive function deficits in high-functioning autistic individuals:relationship to theory of mind. *Journal of Child Psychology and Psychiatry and Allied Disciplines 32, 1081–1105.*
68) Garner, J.P., Weisker, S.M., Dufour, B. and Mench, J.A. (2004b) Barbering (fur and whisker trimming) by laboratory mice as a model of human trichotillomania and obsessive– compulsive spectrum disorders.
Comparative Medicine 54, 216–224.

69) Owen, A.M., Roberts, A.C., Hodges, J.R., Summers, B.A., Polkey, C.E. and Robbins,T.W. 1993. Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease.*Brain 116, 1159–1175.*
70)Kaulfuss, P., Wuerbel, H., failing, K. 2010. *European veterinary behaviourcongress : Papers. Pp.93-96*
71)Baldessarini, R.J. 1996. Drugs and the treatment of psychiatric disorders, depression and mania. In: *Horwitz, D.F., Mills, D.S. 2009. BSAVA manuel of canine and feline behavioural medicine. Second edition. 236-244*
72)Dodman, N.H., Shuster, L., White, S.D., Court, M.H., Parker, D., Dixon, R. 1988. Use of narcotic antagonists to modify stereotypic self-licking, self-chewing, and scratching behaviour in dogs. In: *Horwitz, D.F., Mills, D.S. 2009. BSAVA manuel of canine and feline behavioural medicine. Second edition. 236-244*
73)Vermeire S, Audenaert K, De Meester R, Vandermeulen E, Waelbers T, De Spiegeleer B, Eersels J, Dobbeleir A, Peremans K. 2012. Serotonin 2A receptor, serotoning transporter and dopamine transporter alterations in dogs with compulsive behaviour as a promising model for human obsessive-compulsive disorder. *Psychiatry Res. 2012 Jan 30;201(1):78-87. Epub 2012 Jan 27.*
74)Cooper, J.J., Albentosa, M.J., (2005) Behavioural adaptation in the domestic horse: potential role of apparently abnormal responses including stereotypic behaviour. *Livestock Production Science 92 (2005) 177–182*
75) Dodman, N.H. 1997. The dog who loved too much.Tales, Treatments and the Psychology of Dogs.*Pp. 191-251*
76) Dodman, N.H. Holden, C., Travis, J,. 2010. Can dogs behaving badly suggest a new way to treat OCD? *Science.Vol. 329.*
77)Lewis, M.H., Tanimura, Y., Lee, L.W., Bodfish, J.W. 2007. Animal models of restricted repetitive behaviour in autism.Behavioural brain research 176 66-74.
78)Garner, J.P., Meehan, C.L., Mench, J.A. 2003. Sterotypies in caged parrots, schizophrenia and autism: evidence for a common mechanism. *Behavioural brain research 145 (2003) 125-134.*
79)Moon-Fanelli, A.A., Dodman, N.H. 1998. Description and development of compulsive tail chasing in terriers and response to clomipramine treatment. *J am Vet Med Assoc 1998. 212: 1252-1257.*
8078)Dodman, N.H., Knowles, K.E., Shuster, L. Moon-Fanelli, A.A., Tidwell, A.S., Keen, C.L. 1996. Behavioural changes associated with suspected complex partial seizures in Bull Terriers. *J Am Vet Med Assoc. 1996;208:688-691.*
81)Maletzky, B.M. 1973. The episodic dyscontrol syndrome.*Disorders of the Nervous System 34 : 178-85*
82)Moon-Fanelli, A.A., Dodman, N.H., Famula, T.R., Cottam, N.C. 2011. Characteristics of compulsive tail chasing and associated risk factors in Bull Terriers. *JAVMA, Vol. 238. No. 7*
83)Hollander, E., Anagnostou, E., Chaplin, W., Esposito, W., Haznedar, M., Licalzi, E., Wasserman, S., Soorya, L., Buchsbaum, M. 2005. Striatal volume on magnetic resonance imaging and repetitive behaviours in autism.*Biol. Psychiat. 58:226-32*
84) Reiss, A.L., Abrams, M.T., Greenlaw, R., Freund, L., Denckla, M.B., 1995. Neurodevelopmental effects of the FMR-1 full mutation in humans. *Nat Med. 1:159-67*
85) Sears, L.L., Vest, C., Mohamed, S., Bailey, J., Ranson, B.J., Priven, J. 1999. An MRI Study of the basal ganglia in autism.*ProgNeuropsychopharmacol. BiolPsychiat 23:613-24*
86)Overall. K.L. 2000.Natural animal models of human psychiatric conditions: Assessment of mechanism and validity. *Neuro-Psychopharmacol.&Biol.Psychiat.*V2ol*0. 0204,*,p p. 727-776
87)Fox, M.W. 1966. A syndrome in the dog resembling human infantile autism.*B. Vet. Med.*
88) Panksepp, J., Conner, R., Forster, P.K., Bishop, P., Scott, J.P. 1983. Opiod effects on social behaviour of kennel dogs. *Applied Animal Ethology,* 10 (1983) *63-74*
89) Insel, T.R., Mueller, E.A., Alterman, I., Linnoila, M., Murphy, D.L., 1985. Obsessive – Compulsive Disorder and Serotonin: Is there a connection? *Biol. Psychiatry. 20. 1174-1188*
90) http://altered-states.net/barry/newsletter185/index.htm