Cognition in psychiatry:

pitfalls and caveats in translating a complex clinical disorder to a behavioral animal model

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Learning outcomes:

1	What is translational research?
2	Why does a translational approach to research requires in-depth practical knowledge about the everyday problems faced within the clinic?
3	What are the three broad clinical domains that a translational approach can be applied to?

Translational research in medicine is any sort of of scientific research that facilitates the translation of empirical findings from basic science to practical applications within a clinical setting. Although the fundamental idea is that results from the lab bench should be applied to a practical everyday clinical problem one ought to emphasize that a translational approach really requires that the individuals involved in making the basic research are well acquainted with the practical problems faced in the everyday situation at the clinic. Simply stating that results generated by your basic research could have clinical implications is not really an example of using a translational approach.

A translational approach requires first that the exact nature of the clinical problem to-be-solved is specified, examples from psychiatry with concrete goals could for example be: finding the optimal dose for a specific pharmacological treatment, improve assessment and diagnostic criteria, prevention by slowing down the pathophysiological process, minimize the time in treatment for a therapeutic intervention, or reducing adverse side effects for a specific kind of treatment.

Of course these specific goals require that the researcher is familiar with the symptoms of the disease and how these symptoms are assessed. Basically how diagnosis is done. It is therefore natural that we first turn to the topic of diagnosis and assessment and later on turn to the issue of what causes these disorders (the etiology and pathophysiology). As we will see very little about the etiology and pathophysiology of psychiatric disorders are known and treatment is therefore focused on symptoms. In conclusion, diagnosis/assessment, as well as treatment and etiology are the the three broad areas of clinical practice that a scientist from the basic sciences who intends to do translational research needs to be acquainted with. Given a basic background about diagnosis within psychiatry it will hopefully be apparent that knowledge about how behavior is generated and the underlying lawfulness, as well as randomness, behind the principles of behavior is important in producing translational models of psychiatric disorders. We therefore turn to cognition as a possible stepping stone in translating highly complex psychiatric disorders into more easily studied behavioral components.

Summary:
In this section we introduced the concept of translational research as any sort of of scientific research that facilitates the translation of empirical findings from basic science to practical applications. We emphasized the importance of being well acquainted with clinical problems for a successful translational approach since knowledge about specific problems will translate into specific research questions. We then introduced the three main areas of translation as diagnosis/assessment, etiology and treatment.

2

Diagnosis & Assessment

Learning outcomes:

1	How are mental disorders diagnosed and why are they diagnosed it this way?
2	Mention four main problems DSM has when used as a research tool today.

To diagnose something means to examine a set of symptoms and based on this information identify the nature of an illness or a disorder. Diagnostic classification within psychiatry is the object of unrelenting criticism. This criticism comes from a wide variety of sources. Clinicians often point out that the categories ignore crucial aspects of many patients' problems. Lecturers at universities often points out that reification of diagnoses leads medical students to neglect important clinical aspects and instead learns them to apply a kind of stereotypical thinking that is often not valid when diagnosing patients' symptoms. Basic researchers often point out that the diagnostic categories do not map well onto neuroscientific hypothesis. Laymen are often skeptical against classification systems based on agreement within committees. It is important to be aware about this criticism which largely shaped the way mental disorders are diagnosed today.

I the US the debate over the reality of mental illness reached its peak when a psychologist named David Rosenhan published a paper entitled '*On Being Sane in Insane Places*' in the high impact journal *Science* (Rosenhan, 1973). Rosenhan and a couple of friends found the current diagnostic system in psychiatry highly unsatisfying from an objective and scientific view point. Although the purpose of the experiment was also to open up a larger debate about the unethical treatment of patients rights, an ongoing debate which culminated in the subsequent movie adaptation of the novel *One Flew Over the Coocos Nest* as well as the protests and the subsequent decision by the American Psychiatric Association to remove homosexuality as a mental disorder.

Rosenhan's first experiment (referred to as the pseudopatient experiment) was very simple: since the diagnostic criteria at the time was so vague he argued that if they would show up at different mental institutions around the US and act completely normal except for the case that they would claim to hear a sound that said "thud" they might be diagnosed as mentally insane. The result of the experiment was even surprising to Rosenhan himself: all of the confederates in the experiments were admitted and declared as suffering from a mental disorder. Even more staggering is the fact that after being admitted to the mental institutions all confederates acted completely normal and said they didn't hear the sound anymore, regardless of this the average participant was kept institutionalized for on average 19 days up to a maximum of 52 days (Rosenhan, 1973). When these results were published in the journal *Science* this created an outrage among the psychiatric community and

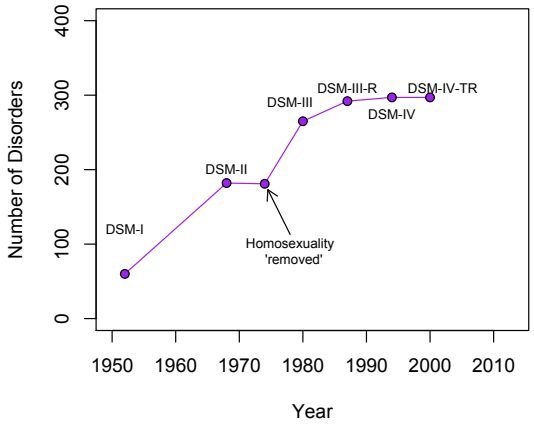


Figure 2.1: Development of the number of major disorders listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM). In 1974 the yearly convention of the American Psychiatric Association was stormed by gay and lesbian activists and as a result the committee changed their minds and dropped one major diagnosis, leaving just 181 in DSM-II (amended) . Before 1974, medical professionals assured us that *"ego-dystonic homosexuality"* was a (treatable) disorder. From 1974, it was reclassified as a "*sexual orientation disturbance*" so it was not completely removed until 1980. Note the impact of Rosenhan's experiment (1974) on the subsequent revision made by Robert Spitzer and Jospeh Fleiss in 1980.

Rosenhan was accused of trickery. In a follow-up experiment published in the same article (referred to as the non-existent impostor experiment) Rosenhan was challenged by a well-known research and teaching hospital which claimed that similar errors could not be made by their prestigious institution (Rosenhan, 1973). Rosenhan arranged with the hospital that during a period of three months, one or more confederates would attempt to gain admission and the staff would provide ratings for every incoming patient as to the likelihood they were an impostor. At the end of the three month period the hospital announced that out of a total sample of 193 patients, 41 were judged to be impostors and an additional 42 were considered as almost qualifying for being an impostor. In reality, Rosenhan had sent no one and all patients suspected as impostors by the hospital were ordinary patients seeking health care. Hence the ability to correctly

A year after Rosenhan's paper was published a psychiatrist named Robert Spitzer and a biostatistican named Joseph Fleiss co-authored an influential paper (Spitzer and Fleiss, 1974) that statistically pointed out the obvious problems with the diagnostic manual when it comes to interrater reliability, that is how much two or more individuals tend to agree in their assessment of a psychiatric diagnosis. Spitzer and Fleiss (Spitzer and Fleiss, 1974; Spitzer, 1975) argued that the purpose of a diagnostic manual is to facilitate communication between individuals such as health professionals and patients about clinical features, etiology, course of illness and treatment. In addition Spitzer and Fleiss argued that the extent to which a concept or measurement is well-founded and corresponds accurately to the real world (what is referred to as the validity of an assessment), can never be stronger than the consistency of the assessment across different practitioners, that is the reliability of the assessment. Hence, according to Spitzer and Fleiss what a diagnostic manual in psychiatry needed was to move away from defining diagnostic criteria from the subjective opinions or hunches of the clinician and simply make the categories so well defined on observable behavior that anyone with sufficient training can agree. This is why psychiatric diagnostic systems, such as the Diagnostic Statistical Manual for Mental Disorders (DSM), (APA, 2000), these days are defined in terms of a large check list of different behavioral criteria (see Table 2.1 for an example).

It is important to be modest in ones critique of psychiatry: to be aware of the changing nature of psychiatric disorders but at the same time not step over the boundary and glorify mental illness as a form of genius repressed by modern society and medicine. As anyone who suffered or met people who suffered from a mental illness can verify the suffering is just as real as any other disorder or illness and society must take this suffering seriously. Therefore clinicians often talk about 'the three Ds': **d**istress, **d**eviant and **d**ysfunction. A mental disorder needs to be distressful for the one who suffers from it, it must be deviant from a normative perspective and it needs to be dysfunctional in the sense that it hinders the patient from being a fully functional individual in everyday activities such as work.

Table 2.1: **DSM-IV-TR Diagnostic Criteria for Major Depressive Episode**

A.	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure (anhedonia). **Note:** Do not include symptoms that are clearly due to general medical condition, or mood-incongruent delusions or hallucinations.
(1)	Depressed mood most of the day, as indicated by either subjective report (e.g., feels sad or empty) or observationn made by others (e.g., appears tearful) **Note:** In children and adolescents, can be irritable mood.
(2)	Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly everyday (as indicated by either subjective account or observations made by others).
(3)	Significant weight loss when not dieting or weight gain (e.g. change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
(4)	Insomnia or hyper insomnia nearly every day
(5)	Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
(6)	Fatigue or loss of energy nearly every day.
(7)	Fatigue or loss of energy nearly every day.
(8)	Diminished ability to think or concentrate, or indecisiveness, nearly every day (indicated by either subjective account or observations made by others).
(9)	Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B.	The symptoms do not meet criteria for mixed episode.
C.	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D.	The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).
E.	The symptoms are not better accounted for by bereavement, i.e., after loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.
	(APA, 2000)

Psychiatry now recognizes that in order to keep the DSM updated with changes in society it needs to maintain a revision from time to time. The method the DSM is revised is called expert consensus agreement, the experts are a task force from the American Psychiatric Association. The current version is the DSM-IV-TR (fourth edition, text revision), (APA, 2000). It is organized into a five-part 'axis' system, with the first axis incorporating 'clinical disorders' and the second covering personality disorders and intellectual disabilities. The remaining axes cover related medical, psychosocial and environmental factors, as well as assessments of functioning for children.

Despite this, the DSM has obvious problems from a research perspective. To start with most of the diagnostic classes are too heterogeneous and this is actually a direct consequence of how the assessment is made. For example, Major Depressive Disorder includes the criteria that the patient should exhibit low mood, inability to feel pleasure (anhedonia), or both for two weeks, and have a total of at least five of nine possible symptoms (see Table 2.1). Hence the diagnosis requires that a given patient present with a certain threshold number of symptoms. An excellent question regarding the heterogeneity will then be how many unique sets of symptoms meet diagnostic criteria for Major Depressive Disorder. We can find this out by using the following equation for computing all possible number of configurations of symptoms without repetitions (symptoms can not be repeated in the sense that you cannot have the same symptom twice or more at the same time):

$$C(n,i) = \sum_{r=i}^{n} \frac{n!}{r!(n-r)!} \tag{2.1}$$

Where n is the number of symptoms to choose from and r is the number of unique symptoms the patient must exhibit. Note that $n!$ means factorial, i.e. $5! = 5 \times 4 \times 3 \times 2 \times 1 = 120$. Hence the possible number of unique sets of symptoms for major depression is:

$$2 \times C(7,4) + C(7,3) = 227 \tag{2.2}$$

That is there exist 227 unique set of symptoms. The situation with Major Depressive Disorder got even worse with the introduction of DSM-IV which included a set of 'specifiers' for MDD which can be thought as forms of subtypes of depression in such a way that any of the symptoms can be further specified with one of the following specifiers:

1. no specifier;
2. chronic;
3. with catatonic features;
4. with melancholic features;
5. with atypical features;
6. with postpartum onset.

This extends the number of unique set of symptoms with a factor of six hence we get 1,362 unique ways to be depressed. If we ad to this that some of the core symptoms are specified in such a way that they are mutually exclusive, for example it is impossible to both have weight gain and weight loss simultaneously, we'll end up with 34,224 possible different combinations. It will of course be self-evident that all of these possible combinations are not equally likely. However, despite containing the term "statistical" in its name the DSM doesn't provide robust statistics for the distribution of patients across all the possible combinations of symptoms.

The picture becomes even more complicated since psychiatric disorders out in the real world are seldom as neatly fitted into discrete categories with well defined boundaries. Comorbidity, the simultaneous presence of two or more medical conditions, is abundant in a psychiatric setting: patients often have multiple psychiatric conditions as well as somatic disorders. In essence this reflects at some point the fuzzy boundary between different diagnostic categories.

In addition to the discrete cases of diagnostic classes the DSM also includes a rating scale called Global Assessment of Functioning (GAF) where the symptom severity on a scale of 0 to 100 in how everyday functioning is affected is assessed. Even though the GAF provides a quantitative measure of the symptom severity the GAF is designed to be applicable to all of the diagnoses contained in the DSM which of course makes it very crude. Because of this it is often common both in the

clinic as well as in research to use specific measurement scales designed to address diagnosis specific symptoms and their severity. Examples of these scales include Montgomery Depression Rating Scale (MADRAS) or Hamilton Depression Rating Scale (HDRS) for major depression disorder, YaleBrown Obsessive Compulsive Scale (Y-BOCS) for Obsessive Compulsive Disorder, (OCD) Panic Disorder Severity Scale (PDSS) for panic disorder, or the Liebowitz Social Anxiety Scale (LSAS) for ratings of symptom severity in social phobia just to mention a few of the most common ones. In most clinical trials these rating scales are often more important outcome measures than whether or not the patient still

In conclusion, the main problem with psychiatric diagnostic classification used to be its reliability, this problem has somewhat been resolved by the work of Robert Spitzer and Joseph Fleiss (Spitzer and Fleiss, 1974; Spitzer, 1975). Nevertheless, problems with applying DSM in a research setting still exist: the built in heterogeneity among the diagnostic classes, the comorbidity seen among real patients, as well as the fuzzy boundaries between different diagnoses, and finally that most diagnostic classes within the DSM does not mention symptom severity and available assessment of functioning on a graded scale (GAF) are often not specific enough.

Summary:
In this section we defined the concept of diagnosis and gave the necessary historical background in order to understand why the Diagnostic Statistical Manual for Mental Disorders (DSM), (APA, 2000), is defined by a list of symptoms rather than by the etiology or pathophysiology of the disease. We then pointed to some specific pit-falls any preclinical attempt in translating these diagnostic categories faces: heterogeneity, comorbidity, fuzzy boundaries, and lack of measures of symptom severity.

3

Etiology & pathophysiology

> "*Contemporary Western medicine is likened to a well-organized, heroic, and technologically sophisticated effort to pull drowning people out of a raging river. Devotedly engaged in this task, often quite well rewarded, the establishment members never raise their ease or minds to inquire upstream, around the bend in the river, about who or what is pushing all these people in*".
>
> (Antonovsky, 1987, p. 87)

Learning outcomes:

1	What is the difference between the etiology and the pathophysiology of a disorder?
2	In your own opinion is it necessary to know the cause of a disorder in order to treat it?

As was apparent in the previous section the diagnostic classification system DSM is explicit on avoiding any reference to possible etiology or pathophysiology. This is because of three reasons (1) either no etiology is known (2) the symptoms can be caused by a range of different things (3) if traumatic events have caused the disorder (such a being in an accident) then it will be difficult, next to impossible, to accurately assess this and the main purpose of the DSM is that raters should agree in their conclusions. Therefore an important avenue for preclinical research is to come up with etiological models.

Etiology refers to the set of causes of a disease or medical condition. Pathophysiology, on the other hand, refers to disordered physiological process associated with a disorder or disease. The quote by social psychologist Aaron Antonovsky made above clearly demonstrates the difference between etiology and pathophysiology. At one level the cause of diabetes is high blood sugar caused by either the inability of the pancreas to produce insulin, or because the cells do not respond to the insulin that is produced. That is the pathophysiology of diabetes. Nevertheless, as Antonovsky argues medicine must also start looking on why these individuals end up with diabetes to start with (who or what is throwing them into the river) and here life style, environmental issues and social factors will be important. Important if not for why individuals end up in a medical condition then for why these individuals remain in that medical condition. In summary etiology not only is restricted to the pathophysiology but must also include environmental and social factors.

As mentioned before the DSM is explicitly designed to not mention any etiology or pathophysiology other than symptoms that arise through well established pathophysiology (like hypothyroidism as a differential diagnosis to depression). Therefore more and more focus is placed on the mechanism behind generating behavior since knowing the mechanism would provide an intermediate step between pathophysiology and complex clinical symptoms. In the next section will will turn to the topic of treatment and the different avenues available when applying a translational approach and after this we will look closer on the topic of cognition and animal models of human behavior.

Summary:
In this section we introduced the concepts of etiology and pathophysiology and we pointed out that very little is known about the etiology of psychiatric disorders. Etiology is defined as the set of causes of a disease or medical condition. Pathophysiology is a set of causes directly related to the disordered physiological processes in a disorder or disease.

4 Treatment

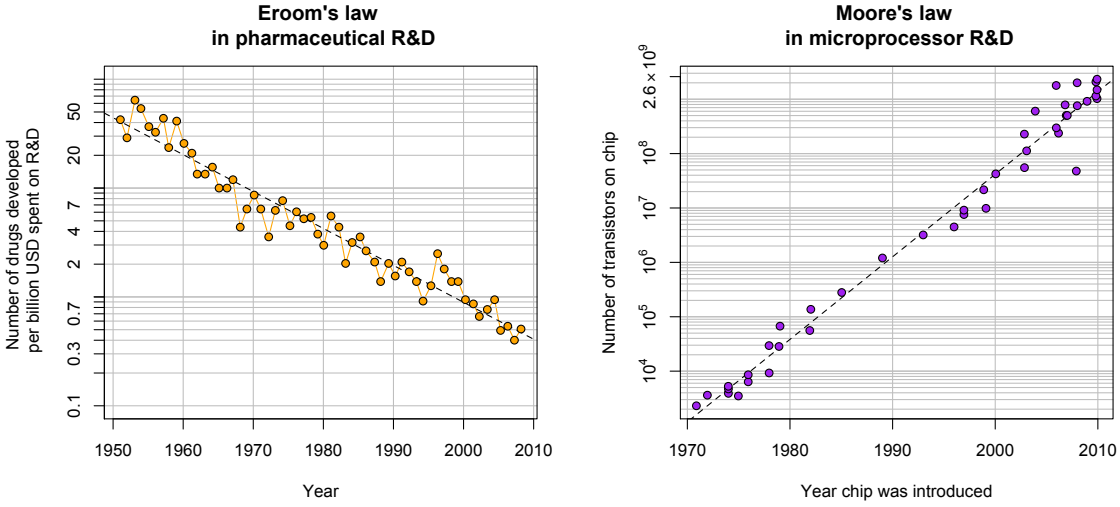
Learning outcomes:

1	What is the difference between treatment and prevention?
2	Give examples of how basic research could optimize treatments already available?

4.1 Drug discovery

Most of the time preclinical research has been focused on drug discovery. At the point where several large pharmaceutical companies are closing down their Research and Development (R&D) for psychiatric drugs I think it is important to critically examine what is likely to work, and more importantly what is unlikely to ever be successful in terms of drug discovery for psychiatric disorders. Let us start with a simple fact: R&D in the pharmaceutical industry has most of the time been completely unsuccessful. For example, compare R&D results in pharmaceutical industry with R&D in the electronic industry or other fields that appeared during the later half of the last century. In Figure 4.1 left panel we can clearly see the decline in the number of new drugs per billion USD spent on R&D (controlled for inflation). This is known as Eroom's law (Scannell et al., 2012) which is simply Moore's law spelled backwards. Moore's law on the other hand refers to the great improvement every second year in terms of computational power (the number of transistors per microprocessor chip doubles every second year, see Figure 4.1 right panel). Just a couple of years ago it would have been hard to imagine the computational power of smartphones or even to stream high definition video on the internet. We have not even seen anything similar to this in pharmaceutical development. Note for example that there is a small upswing in the middle of the 1990s. One might think this is due to the first wave of biotechnology (e.g., transgenic mice strains, computational drug design etc.). It turns out that the small upswing cannot be attributed to true R&D progress (Scannell et al., 2012) but is rather the result of the american Food and Drug Administration (FDA) clearing a backlog due to a law called Prescription Drug User Fee Act which made it possible for FDA to collect a fee for processing applications which then reduced the approval time for non-priority drugs from 27 months to 14 months (Scannell et al., 2012). Hence the small peak in the 1990s cannot be attributed to the wast technological breakthroughs of transgenic mice strains, biotechnology, or computational drug design and screening but is rather a result from legislation and bureaucracy.

Figure 4.1: **Left:** Eroom's Law (Moore's Law backwards): the number of new drugs approved per inflation corrected USD billion on R&D has halved every 9 years since 1950. **Right:** Moore's law is the observation that over the history of computing hardware, the number of transistors on integrated circuits doubles approximately every two years.



So the costs for developing drugs are increasing but the number of new drugs released are basically flat and even decreasing. It is important to note that this is probably not due to the fact that there are no effective drugs to be discovered anymore. Rather the pharmaceutical industry has very strong incentives to only favor R&D on compounds that can be protected by a patent and therefore yield a profit. Norberg et al. (2008) reviewed the extensive literature which demonstrates that taking the cognitive enhancer D-Cycloserine just before exposure based therapy sessions boosts the performance of the exposure therapy for numerous anxiety related disorders (Norberg et al., 2008). Nevertheless D-Cycloserine is unlikely to ever receive the attention from big pharma since D-Cycloserine was originally developed early in the last century as an antibiotic effective against *Mycobacterium tuberculosis* and hence it cannot be patented by any pharmaceutical company. The mechanism of D-Cycloserine in psychotherapy is thought to be unrelated to its role as an antibiotic but rather related to its role as a NMDA partial agonist of the glycine site which indirectly increases glutamatergic activity. In conclusion, at the moment there does not exists proper funding or incentive for doing research on 'drug discovery' which is likely to generate and improve therapy for psychiatric disorders.

4.2 Prevention

Why should preclinical research bother with prevention at all isn't prevention more the avenue for policy makers and politicians? If you are tempted into believing this consider for example the case of Alzheimer's Disease (AD). Most preclinical research into AD is focused on one thing and one thing only: finding the cause of AD. At the moment most efforts are directed at beta amyloid palques despite the fact that old people with perfect cognitive aging (centarians) can have large deposits of amyloid plaque without even a slightest indication of cognitive decline. What if preclinical research would be more focused on developing methods for early diagnosis and slow down of the cognitive decline in AD rather than trying to find 'the cure' for AD? If one would be able to find a way to postpone the disease onset (incidence) by just a couple of years the result would actually be staggering. We know that AD is an age related disease: most people who get affected are old. However, it is less commonly known that the incidence rates of the disease doubles in the population every five year of aging (Jorm et al., 1987). Hence if one would be able to diagnose the disease early, before symptoms have started to appear, and are able to direct treatment options that can

postpone and slow down the cognitive decline by as little as 5 years on average one would decrease the prevalence of AD in the population by a staggering number of 50%.

4.3 Treatment optimization

As previously mentioned more and more clinical researchers within academia have started to examine different drugs that could boost or improve the effect of effective treatments already available such as psychotherapy. For several anxiety disorders D-Cycloserine administrated together with traditional exposure based therapy has proved to boost the treatment effect of exposure based therapy as well as minimize the number of exposure sessions it takes to get a specific treatment response (Norberg et al., 2008). Nevertheless, the drug has several problems such as high tolerance and large individual differences in treatment outcome.

Other examples from psychiatry where basic research has enabled better optimization of therapies include the initial studies of D_2 receptor occupancy by the antipsychotic agent haloperidol (Nyberg et al., 1995). Haloperidol a typical antipsychotic which already proved to be effective in the treatment of positive symptoms and prevention of psychotic relapses has several side effects such as extra pyramidal symptoms, cognitive impairment, akinesia, and dysphoria. The risk of these side effects are often dose related and therefore it is crucial to find the optimum dose. It is generally agreed that the effect of haloperidol is due to its high affinity for D_2 receptors (Nyberg et al., 1995).. Using Positron Emission Tomography (PET) and Nyberg et al. (1995) and colleagues were able to find that the optimal receptor occupancy was at levels considerable lower than indicated by current medication practices in the dose prescribed to patients. This study (Nyberg et al., 1995) provided an important incentive for changing current prescription policies and therefore helped thousands of patients getting treatments with considerably less side effects than before.

Summary:
In this section we looked more in-depth on three specific areas related to treatment: drug discovery, prevention and treatment optimization. Although the number of new drugs per billion USD spent of R&D has declined steadily since the 1950s there exist interesting avenues for development such as D-Cycloserine, as well as prevention and early diagnosis of neurodegenerative disorders such as Alzheimer's Disease. We also took a closer look on studies aimed at optimizing the prescribed dose of haloperidol in schizophrenia to elevate the extra pyramidal side effects.

5

Cognition, mood and emotions

Learning outcomes:

1	What is cognition?
2	How does cognition differ from non-cognitive mental processes or states?

Cognition refers to any mental action or process by which we acquire knowledge about the external world through thought, experience or our senses. Examples of cognitive faculties include memory, perception and attention among others. It is important to differentiate cognition from other non-cognitive processes such as emotions, mood or sensations. Pain is a sensation, although becoming aware that the pain is localized for example in the stomach or the leg is an act of cognition (tactile perception) feeling pain itself is not. The reason why the sensation of pain is not a cognitive process is because simply feeling something is not acquiring knowledge about anything. Similarly being in a mental state such as being sad or happy is neither examples of cognitive processes. That is not to say that these mental states do not affect cognitive processes; being in pain clearly affects both attention, perception and memory the same can be said about mood and emotions such as anger or sorrow.

Some psychiatric disorders are even defined in terms of a cognitive profile such as Attention Deficit Disorder (ADD) which is often characterized by marked reduced selective attention compared to other cognitive domains such as reading comprehension or problem solving. Other psychiatric disorders such as social phobia or depression are characterized by specific ways to processes certain information (so called processing biases). Social phobics are more likely to interpret their actions in a social situation as targeted by criticism from others, whereas patients suffering form depression have a negative explanatory style about events in general. Understanding these cognitive processes and how they come to differ in mental disorders could provide a stepping stone in translating a complex psychiatric condition into a more manageable preclinical model. In the next section we will turn to some of the most common animal models of cognitive processes, mood and emotions.

Summary:

In this section we defined the concept of cognition as any mental action or process by which we acquire knowledge about the external world through thought, experience or our senses. We then contrasted cognition against non-cognitive processes such as pain sensation or emotions and mood which, unlike pure cognitive processes, are not intentionally about acquiring knowledge.

6

Common animal models of psychiatric disorders

Learning outcomes:

1	The student is in no way forced to memorize all of these tasks but should be able to recognize them since they are commonly used within the literature. Hopefully this section can be used as a desktop reference for the student in the future.

6.1 5-Choice Serial Reaction Time Task

The 5-Choice Serial Reaction Time Task (5-CSRTT) is a paradigm for measuring attention and working memory in rodents (Robbins, 2002). It has also been used to measure impulsivity. The 5SCRTT uses a 9-hole apparatus that gives the rodent a brief 0.5 second visual stimulus which acts as a cue. The rodent is then trained to nose poke in the just illuminated hole. Measures include the reaction time and accuracy of the rodent's responses, and categorizing the types of errors made by the rodent (omission, commission). Has been used to model symptoms in everything ranging from schizophrenia to ADHD.

6.2 Prepulse inhibition

A common model of a sensory motoric gating deficit seen among schizophrenic patients. In a PPI test one elicits the startle reflex (full body startle in rodents or contraction of the *orbicularis oculi* muscle around the eye in the case of humans) by a loud ($\sim$ 90 dB) and short burst (50 ms) of white noise. If the subject is presented with a not as loud sound pulse (prepulse) just before one elicits the startle reflex with the louder sound pulse (called probe) one will observe that the startle reflex magnitude is decreased indicating that the brain is prepared to process the startle eliciting pulse. In schizophrenics this prepulse inhibition is greatly reduced and this has been related to dopaminergic transmission which is one of the main targets for antipsychotic drugs (Swerdlow et al., 2008). This prepulse inhibition deficit is thought to reflect a fundamental attention deficit in schizophrenia.

6.3 Delayed Matching to Sample

A memory test which can be done both in humans and rodents. The subject is trained to identify a specific cue with a specific target stimulus then when the cue is presented the target is presented together with a distractor stimulus after a short delay between cue and target (Blough, 1959). The task of the animal is to chose the target stimulus rather than the distractor and the delay makes sure that the subject keeps the representation of the cue in memory.

6.4 Object recognition test

In this test a small object is placed together with the animal in a chamber. After initial exploration the animal is removed. At a later time the animal is then presented with the previous object together with a completely novel object, if the animal remember the previous object it will demonstrate an exploratory preference for the novel object (Antunes and Biala, 2012). This test is used as a measurement of memory in human infants as well.

6.5 Morris water maze

A spatial learning task where the animal swims around to find a platform that is hidden a few millimeters bellow the surface (Morris, 1981). Often one puts color into the water so the animal cannot identify the platform with vision alone. After repeating the procedure for several days the animal will learn the location of the platform as indicated by a decrease in the distance the rodent swam.

6.6 Rotarod task

A simple task to test motor behavior. The animals are placed on a rod that starts to rotate and the animal will start moving in order to not fall down from the rod. Has been used as a test of models for Parkinson's Disease.

6.7 Peak-Interval Procedure

A model that has been used in studying Parkinson's Disease and schizophrenia (Gibbon et al., 1997). Peak-interval (PI) procedure is a psychophysical production taskthat consist of two types of trials randomly intermixed: in fixed-interval trials, the organism's responses are reinforced at the to-be-timed duration, e.g. a Fixed-Interval 20s reinforcement schedule (FI:20) means that the first response made after 20 seconds from cue onset is reinforced. The other type of trials are called peak trials, the organism is required to respond at the to-be-timed duration, but no reinforcement is available and the cue is extended normally three times the duration to-be-timed. The typical result is that the distribution of responses in peak trials is centered around the criterion duration, with a standard deviation proportional to this criterion. The PI procedure offers multiple measurements that are sensitive to striatal circuit function (Gibbon et al., 1997). The absolute response rate and it's decline as the to-be-timed interval is increased gives a measurement of motivation and temporal discounting. Start and stop times on each individual trial gives a measurement of both impulsivity as well as properties related to the processing of the temporal information (i.e. clock speed, accuracy). As stated before is commonly observed that responding during peak trials where the response rate is normalized follows a Gaussian distribution with the peak centered at the to-be-timed duration and variance proportional to the interval to-be-timed, known as the *scalar property* or *Weber's law* of interval timing (Gibbon et al., 1997).

6.8 Elevated Plus Maze

Is a rodent model of anxiety that is used as a screeningtest for anxiolytic or anxiogenic compounds and as a general research tool in anxiety research (Pellow et al., 1985). The test setting consists of a plus-shaped apparatus with two open and two enclosed arms, each with an open roof, elevated 4070cm from the floor. The model is based on rodents' aversion of open spaces. This aversion leads to avoidance of open areas by confining movements to enclosed arms. This measurement of anxiety has been shown to be affect by benzodiazepines but not other drugs common in treatment of anxiety such as SSRI. Benzodiazepines are not anxiolytic specific but also give general sedative effects and blunts other emotions as well which is a problem for the validation of the task as an anxiety specific measurement. In addition, benzodiazepines are seldom recommended for anxiety disorders since they are highly addictive.

6.9 Open Field Activity

A measure of general locomotor activity and willingness to explore in rodents (Hall and Ballachey, 1932). Locomotoric activity is measured in time spent moving and anxiety related measures are obtain by observing the relative preference towards navigating near the walls of the open field and avoiding the center zone where the mouse feels unsafe.

6.10 Fear Conditioning

A neutral stimulus is presented contingently with a unconditioned stimulus that is aversive such as an electric shock and after a while the neutral stimulus itself will elicit a fear response when presented alone indicating that fear has been learnt. This model is often thought to reflect the etiological model behind exposure based psychotherapy (Watson and Rayner, 1920). Therefore exposure based psychotherapy is built around the principle that the learnt association between fear and previous neutral stimuli needs to be extinguished through repeated exposure to the stimulus. The startle reflex can be increased in magnitude via fear conditioning (called fear-potentiated startle) and therefore serves as a translational measurement between rodents and humans since both rodents and humans have the startle reflex. It is however more common in rodents to measure the percentage of individuals that are freezing during specific periods when the fear conditioned stimulus is presented.

6.11 Learned helplessness

A condition and an experimental paradigm for the study of depression where the animal cannot escape electric shocks and after a while will learn that it cannot prevent the shocks from coming and will give up any attempt in avoiding the shock (Seligman and Maier, 1967).

6.12 Forced Swim Test

Rodents are put into jars filled with water and the relative duration of struggling to keep above the water versus floating around (immobility) without struggling is thought to reflect similar helplessness as in learned helplessness and this is considered to be a model of depression in rodents.

Summary:
In this section we gave a brief description of the following paradigms: 5-CSRTT (attention, working memory, schizophrenia, ADHD), Prepulse inhibition (sensory motoric gating, schizophrenia), Delayed Matching to Sample (memory, dementia), Object recognition test (memory, dementia, depression), Morris water maze (spatial learning, memory, dementia, depression), Rotarod task (motor function, Parkinson's disease), Peak-Interval Procedure (interval-timing, schizophrenia, Parkinson's disease), Elevated Plus Maze (anxiety disorders), Open Field Activity (locomotion, anxiety disorders), Fear Conditioning (anxiety disorders), Learned helplessness (depression), Forced Swim Test (depression).

A

Appendix: Definitions

Cognition: any mental action or process by which we acquire knowledge about the external world through thought, experience or our senses.

Comorbidity: the simultaneous presence of two or more medical conditions

Etiology: the set of causes of a disease or medical condition.

Information: knowledge which reduces a previous uncertainty.

Knowledge: true justified belief.

Learning: acquisition of knowledge or skills from either experience, study or being taught.

Memory: the mental faculty of retention of knowledge acquired.

Pathophysiology: disordered physiological processes associated with a disorder or disease.

Perception: the ability to become aware about something through the senses.

Reliability: the overall consistency of a measure.

Translational research: any sort of of scientific research that facilitates the translation of empirical findings from basic science to practical applications.

Uncertainty: the state that several plausible scenarios could be true.

Validity: the extent to which a concept, conclusion or measurement is well-founded and corresponds accurately to the real world.

Working memory: the ability to selectively maintain and manipulate information across short durations.

B

Appendix: Chapter summaries

Chapter 1: Introduction
In this section we introduced the concept of translational research as any sort of of scientific research that facilitates the translation of empirical findings from basic science to practical applications. We emphasized the importance of being well acquainted with clinical problems for a successful translational approach since knowledge about specific problems will translate into specific research questions. We then introduced the three main areas of translation as diagnosis/assessment, etiology and treatment.

Chapter 2: Diagnosis & Assessment
In this section we defined the concept of diagnosis and gave the necessary historical background in order to understand why the Diagnostic Statistical Manual for Mental Disorders (DSM), (APA, 2000), is defined by a list of symptoms rather than by the etiology or pathophysiology of the disease. We then pointed to some specific pit-falls any preclinical attempt in translating these diagnostic categories faces: heterogeneity, comorbidity, fuzzy boundaries, and lack of measures of symptom severity.

Chapter 3: Etiology & Pathophysiology
In this section we introduced the concepts of etiology and pathophysiology and we pointed out that very little is known about the etiology of psychiatric disorders. Etiology is defined as the set of causes of a disease or medical condition. Pathophysiology is a set of causes directly related to the disordered physiological processes in a disorder or disease.

Chapter 4: Treatment
In this section we looked more in-depth on three specific areas related to treatment: drug discovery, prevention and treatment optimization. Although the number of new drugs per billion USD spent of R&D has declined steadily since the 1950s there exist interesting avenues for development such as D-Cycloserine, as well as prevention and early diagnosis of neurodegenerative disorders such as Alzheimer's Disease. We also took a closer look on studies aimed at optimizing the prescribed dose of haloperidol in schizophrenia to elevate the extra pyramidal side effects.

Chapter 5: Cognition, mood, and emotions

In this section we defined the concept of cognition as any mental action or process by which we acquire knowledge about the external world through thought, experience or our senses. We then contrasted cognition against non-cognitive processes such as pain sensation or emotions and mood which, unlike pure cognitive processes, are not intentionally about acquiring knowledge.

Chapter 6: Common animal models of psychiatric disorders

In this section we gave a brief description of the following paradigms: 5-CSRTT (attention, working memory, schizophrenia, ADHD), Prepulse inhibition (sensory motoric gating, schizophrenia), Delayed Matching to Sample (memory, dementia), Object recognition test (memory, dementia, depression), Morris water maze (spatial learning, memory, dementia, depression), Rotarod task (motor function, Parkinson's disease), Peak-Interval Procedure (interval-timing, schizophrenia, Parkinson's disease), Elevated Plus Maze (anxiety disorders), Open Field Activity (locomotion, anxiety disorders), Fear Conditioning (anxiety disorders), Learned helplessness (depression), Forced Swim Test (depression).

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