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Article 1: The Spontaneously Hypertensive Rat (SHR) as an Animal Model of Attention-Deficit/Hyperactivity Disorder; Stimulus Control, Sensory Reinforcement and Discrimination

Article 2: Effects of Response Feedback Light: Behavioral Differences Between the Spontaneously Hypertensive Rat (SHR) and Controls

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Table of contents

Abstract for both articles

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder found all over the world with a prevalence of around 5% in children and 2.5% in adults. An estimated heritability of 76% has been suggested, which leaves around 20-25% to be caused by environmental factors or a heredity-environmental interaction. The dynamic developmental theory (DDT) is a theory on ADHD based on studies of an animal model called the spontaneously hypertensive rat (SHR) and suggests that ADHD symptoms are caused by altered reinforcement of novel behavior and deficient extinction of previously learned behavior. Deficit stimulus control or effects of sensory reinforcement may lead to symptoms of ADHD, especially inattention and hyperactivity. In 1992, Sagvolden, Hendley & Knardahl did a study on SHR where they found that by installing a response feedback light above the left lever during extinction in a two-component schedule, the response rate of the SHR increased substantially compared to the other strains. The purpose of the present experiment was to investigate the increased response rate observed in SHR during extinction with the response feedback light, and test whether this activity increase is caused by effects of sensory reinforcement or general discrimination problems. Studies on stimulus control in an animal model may increase the understanding of symptoms and behavior changes observed in children with ADHD.

Keywords: Attention-deficit/hyperactivity disorder, ADHD, The dynamic developmental theory, The spontaneously hypertensive rat, Stimulus control, Sensory reinforcement

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder found in ~5% of all children all over the world and is amongst the most common psychiatric diagnoses in children. The disorder is usually divided in two categories, inattention and hyperactivity/impulsiveness. To get the diagnosis of ADHD at least 5 of the 9 symptoms on either or both categories described in the diagnostic and statistical manual of mental disorders must be observed regularly for six months or more. The causes of ADHD are not sufficiently known. An estimated heritability of 76% has been suggested, but no single gene has been marked as the ADHD gene. The dynamic developmental theory of ADHD (DDT) is a theory of ADHD based on studies of an animal model, the spontaneously hypertensive rat (SHR). An animal model does not completely mimic a human disorder, but they can imitate patterns seen in the human diagnosis and give insight on how variables affect behavior, brain or neurological factors. Since the DDT is based on behavior and to some extent neurobiology, a brief explanation will be given on behavioral analytic theory in this review. A selection of relevant studies will be mentioned in regards to SHR's lack of stimulus control and possible effects of sensory reinforcement. These factors may be important for the understanding of behavior changes in the SHR and in turn the symptoms of ADHD.

Keywords: Attention-deficit/hyperactivity disorder, The dynamic developmental theory, The spontaneously hypertensive rat, Stimulus control, Sensory reinforcement

The Spontaneously Hypertensive Rat (SHR) as an Animal Model of Attention-Deficit/Hyperactivity Disorder; Stimulus Control, Sensory Reinforcement and Discrimination

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder found in both adults and children and is suggested to occur in around 2.5% of all adults and 5% of all children (American Psychiatric Association, 2013). The gender prevalence is higher in males with the ratio being two to one in children and one point six to one in adults (American Psychiatric Association, 2013). ADHD is characterized by patterns of behavior which can be observed in multiple settings ranging from home, school and work to interaction with friends and family and other social settings. These patterns of behavior will negatively affect both educational and/or social performance as well as performance in work related tasks. In the diagnostic and statistical manual of mental disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) ADHD symptoms are divided in two categories, with one category being inattention, and the other category being hyperactivity and impulsivity. In Norway, the non-American diagnostic manual, ICD-10, is used and it does not feature the term ADHD, but rather hyperkinetic disorder (HKD) (Helsedirektoratet, 2011). Since ADHD is a common part of the language also outside America, maybe even more so than HKD, ADHD is preferred for this article. Despite the fact that they have different names, the two diagnoses are basically described the same way. They are both acknowledged as neurodevelopmental disorders with their criteria being behavioral, but also very general descriptions. Although being similar, because of the two categories in DSM-5 it is possible to have ADHD without being inattentive, while inattentiveness is a criterion in ICD-10. Inattention in particular is also found in many other psychiatric disorders, with an exception being mania (Taylor, 1998). Inattention is described as trouble with maintaining attention in situations where this is expected. If a stimulus controls a behavior over time we call it

sustained attention and it has been argued that problems with inattention are the result of changed motivational processes (Sagvolden, Johansen, Aase, & Russell, 2005). Hyperactivity is described as a higher level of activity than normal and impulsiveness is described as the urge to act without thinking or the inability to wait. A dynamic developmental theory has been proposed (Sagvolden, Johansen, et al., 2005) and argues that symptoms of ADHD may be caused by altered reinforcement of novel behavior and deficient extinction of previously reinforced behavior. The dynamic developmental theory also suggests that dopamine hypofunction may reduce the temporal window for correlating preceding stimuli and behavior with the consequences of the behavior (i.e. shorter delay-of-reinforcement gradient) and weakens the extinction of previously learned or unwanted behavior. These processes may be what produces the behavioral symptoms of hyperactivity, inattention and impulsivity (Sagvolden, Aase, Zeiner, & Berger, 1998). There have been proposed several animal models of ADHD, but the most frequently used model is the spontaneously hypertensive rat (SHR) (Sagvolden, 2000). It may possibly also be the best validated animal model of ADHD (Russell, Sagvolden, & Johansen, 2005; Sagvolden, 2000; Sagvolden & Johansen, 2012; Sagvolden, Russell, Aase, Johansen, & Farshbaf, 2005). It was bred from Wistar-Kyoto (WKY) rats for the high blood pressure and spontaneously hypertensive traits (Okamoto & Aoki, 1963) which cause increased behavior responding and hyperactivity. All of the behavior characteristics of ADHD including inattention without any clear sensory problems, overactivity, motor impulsiveness and motor control problems have been observed in SHR (Sagvolden, 2000; Sagvolden, Russell, et al., 2005). Hyperactivity and inattention is not present in novel situations, but will gradually develop over time (Knardahl & Sagvolden, 1979; Sagvolden, Russell, et al., 2005). SHR, compared to controls, is more sensitive to delay of reinforcement (Johansen, Sagvolden, & Kvande, 2005; Sagvolden et al., 2009) with a steepened delay-of-reinforcement (Johansen, Killeen, & Sagvolden, 2007) just like in

humans with ADHD (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). In 1992 Sagvolden and co-workers published an article where they wanted to extend the behavioral characterization of two strains recently developed, the WKHA and WKHY (Hendley, Wessel, & Van Houten, 1986), by comparing them to WKY and SHR (Sagvolden, Hendley, & Knardahl, 1992). Included in the study was a multiple fixed-interval (FI 2-min) extinction (5-min EXT) schedule. During the extinction component with a response feedback light above the left lever they observed a high rate of responding compared to the absence of the response feedback light, in the SHR. They concluded that this response pattern may be because of reinforcing properties in the response feedback light, or discrimination problems between feedback light and tray light in SHR. Other studies have found the same effect with a response feedback light during extinction (Sagvolden, Pettersen, & Larsen, 1993; Wickens, Macfarlane, Booker, & McNaughton, 2004). Generally, sensory reinforcers are said to be weak (Catania, 2013) and stimulus control in SHR has been observed being much lower than in WKY, but no discrimination deficit in SHR relative to WKY has previously been found (Knardahl & Karlsen, 1984). This article will briefly cover the symptoms and etiology of the psychiatric diagnosis of ADHD, briefly review some aspects of the dynamic developmental theory of ADHD and behavior analytic theory as well as describe SHR as an animal model. Further, selected studies of sensory reinforcement and stimulus control in SHR/NCrl will be reviewed. Studies on stimulus control in an animal model may increase the understanding of symptoms and behavior changes observed in children with ADHD.

Discussion

Attention-Deficit/Hyperactivity Disorder

Symptoms. The diagnostic and statistical manual of mental disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) features nine symptoms of hyperactivity/impulsiveness and nine symptoms of inattention where six (five for adults over

the age of 17) or more on either one must have persisted for at least six months for the diagnosis to be fulfilled. It is possible to have either a combined presentation with six symptoms from each category or a predominantly presentation in either category, all leading up to the diagnosis of ADHD (American Psychiatric Association, 2013). It has been suggested that those with a combined presentation have a more severe disorder (Faraone, Biederman, Weber, & Russell, 1998). All of the symptoms are general descriptions of behavior and there is no true test or way to measure them.

Inattention. Inattention is generally understood as trouble with maintaining attention in situations where stimuli are widely spread over time seeking away from tasks for other sensations, for example visual or sound (Taylor, 1998). Compared to others, people with inattention may fail to focus on details in task and instructions, have difficulty organizing tasks, avoids mental tasks, lose important things needed for specific tasks and is often forgetful in daily activities (American Psychiatric Association, 2013).

Hyperactivity. Hyperactivity is described as engaging at a much higher level of activity than what is normal in regards to the situation and/or engaging in activity not suitable for the situation. Examples of this is high rate of tapping or drumming on surfaces, speaking with peers in the classroom and walking about in meetings or during class. People with ADHD, compared to others, will more often switch between tasks as well as finishing them faster, they will show faster movements with the entire body and will generally have trouble sitting still and being restless (Taylor, 1998). Hyperactivity is generally not visible in novel situations (Sagvolden et al., 1998) but develops after some time as the person interacts and with its surroundings and reinforcers increase in those situations (Aase & Johansen, 2010).

Impulsiveness. Impulsiveness can be defined as the urge to act without thinking and having trouble with future planning (Johansen, Aase, Meyer, & Sagvolden, 2002). It has been argued that people with impulsive behavior take more risks and performs more hasty actions

which can lead to low performance in risky situations and increased chance of accidents (Taylor, 1998). An example may be drivers with ADHD who may cut corners, take turns without checking for other cars or drive over the speed limit. Risk-taking may also impact social areas of life like making important decisions such as taking jobs, buying cars and houses and taking drugs without thinking about future consequences. Impulsiveness might be split into two subcategories. Motor impulsiveness and cognitive impulsiveness (Johansen et al., 2002). Motor impulsiveness is described as bursts of responses with short inter-response times (IRT). Short IRTs contribute to ADHD overactivity, but these bursts may as well describe the impulsiveness (Sagvolden et al., 1998). Cognitive impulsiveness is related to problems organizing own behavior as well as rapid shifts of private events like thoughts and plans (Johansen et al., 2002).

Etiology and Diagnosis of ADHD

ADHD can be found all over the world (Faraone, Sergeant, Gillberg, & Biederman, 2003). It is amongst the most common psychiatric diagnoses in children (Aase & Johansen, 2010), but can be found in adults as well. The earlier diagnostic and statistical manuals may not have accurately characterized the symptoms of affected adults. DSM-5 has adapted new criteria for adults ("Attention Deficit / Hyperactivity Disorder," 2013). Adults over 17 years of age can show fewer symptoms than children to be diagnosed with ADHD. This inclusion was done because research showed that adults had the disorder even decades after childhood, but observations also showed that some symptoms were less visible. Generally, ADHD is said to be remitted, or at least lessened in adulthood (Faraone, Biederman, & Mick, 2006), but some studies argue that this is not always true. Faraone and co-workers (2000) did an overview of ADHD in adults where they found support for the diagnostic validity of the disorder in grownups. The causes of ADHD are not sufficiently known other than that the disorder is neurodevelopmental and that it can’t be explained purely by psychosocial

conditions. Results from twin studies suggest that ADHD is among the most heritable psychiatric disorders with an estimated heritability around 76% (Faraone et al., 2005). This suggests that around 20-25% have to be the cause of environmental factors or a heredity-environmental interaction. A study done on South African children (Aase, Meyer, & Sagvolden, 2006), a close replication of one done on children in Norway (Aase & Sagvolden, 2005), made a strong case for ADHD being a neurobehavioral disorder rather than a cultural disorder. Studies done on families, twins and children of adoption give insights into genes that might play an important role in ADHD (Faraone et al., 2005). It would definitely greatly benefit the field of ADHD if the exact genes of the disorder were found. Genetic research is prioritized, but no single gene stands out and although finding many genes associated with ADHD, it has been argued that "genetic vulnerability to ADHD is mediated by many genes of small effect" (Faraone et al., 2005). A selection of the genes argued to show significant evidence of association with ADHD is the dopamine receptors DRD4 and DRD5, the dopamine transporter DAT as well as SNAP-5 (Faraone & Mick, 2010; Faraone et al., 2005). Additionally we may encounter cases with possible damage to the nervous system and great variability – both in symptoms and behavior over different situations and over time. Some human cases suggest a highly plausible genetic cause of ADHD. Still, it is not a 100% correlation and no genetic test exist as of now, so it is still advised that ADHD should be diagnosed by a professional clinician based on the presence of symptoms (American Psychiatric Association, 2013).

A Dynamic Developmental Theory of ADHD

ADHD research covers many areas and levels, including its behavioral symptoms with general cognitive descriptions, genetics, neurobiology and environmental factors. As of now there is no true way to test or measure ADHD directly. One theory was proposed by Sagvolden and co-workers (2005) called the dynamic developmental theory (of attention-

deficit/hyperactivity disorder)(DDT) with its basis in behavior analysis and neurobiology. It is mainly two behavioral processes that form the foundation for the theory and are argued to cause ADHD; altered reinforcement of novel behavior and deficient extinction of previously reinforced behavior. The behavior of normal children and children with ADHD is differently affected by reinforcement contingencies (Douglas & Parry, 1994; Sonuga-Barke et al., 1992) and it has formerly been argued that main symptoms of ADHD may be due to shorter delay-of-reinforcement and altered reinforcement mechanisms (Sagvolden et al., 1998; Sagvolden & Sergeant, 1998). Dopamine is closely linked to the basic mechanics of behavior analysis, reinforcement and extinction. The DDT focuses on dysfunctional dopamine systems as a fundamental factor in developing ADHD. The DDT also takes into account that ADHD-like behavior may be caused by drugs affecting or regulating the dopamine system. Further, the theory emphasize that the ADHD symptoms may to a large extent vary depending on time in life and surrounding environments thus making ADHD dynamic in its manifestation. Although environmental factors may not produce ADHD, they can certainly affect or produce unwanted development of behavior.

Altered reinforcement and extinction processes, "symptoms" of ADHD. The DDT (Johansen et al., 2002; Sagvolden, Johansen, et al., 2005) suggests that learning mechanisms may be different due to a hypofunctioning dopamine system by creating a shorter time window for associating behavior with its antecedent stimuli and its consequences. This may lead to altered reinforcement processes in children or animals with ADHD traits and can be described by a steeper and shorter delay-of-reinforcement gradient and slower extinction of inefficient responses. Since learning takes longer as well as unwanted responses take longer to extinguish, behavior for groups with these deficits is often described as inattentive (lack of stimulus control), impulsive, overactive and variable. ADHD children will have trouble with future planning. Compared to normal children (controls) they are to a greater extent

controlled by immediate reinforcers and their behavior is to a lesser degree controlled by delayed reinforcers. This happens even when immediate reinforcers have lower value than any reinforcer available after delay (Sonuga-Barke et al., 1992). While normal children would seem to maximize profit in reinforcement earnings over time, ADHD children are delay minimizers or might even be delay aversive, trying to reduce overall delay instead of maximizing profit (Sonuga-Barke et al., 1992). It has also been shown that those with ADHD will get more 'frustrated' and perform poorer during intermittent reinforcement and extinction (Douglas & Parry, 1994). That doesn't necessarily mean that there is less behavior overall, but rather that the behavior is spread on different activities or versions of the expected behavior (hyperactivity), and less controlled by reinforcement contingencies (inattention). Theories like the DDT are an important way of understanding ADHD by systemizing data and doing predictions for behavior that can be empirically tested. The DDT approaches ADHD from another point of view than for example the before mentioned DSM. While the DSM declares that symptoms which are complex and consists of strings of impulsiveness, inattention and increase in activity may only be called ADHD if it's not better explained by other disorders like anxiety, personality and mood disorders, it does not provide an explanation or a theory of mechanisms underlying the development of the symptoms for ADHD, like reduction of special senses, medical complications or psychosocial problems (like family issues). The DDT on the other hand embraces these factors and points to the fact that behavior is formable in the way that it might produce or intensify ADHD symptoms or behavior.

Relevant Behavioral Analytic Theory

Since the dynamic developmental theory of attention-deficit/hyperactivity disorder (and behavioral studies of ADHD) is based on behavior analysis, they use a specific set of terms from this science. The three-term contingency (Antecedent stimuli – Behavior –

Consequence) is fundamental in behavior analysis and is a description of a behaviors relation to preceding stimuli and subsequent stimuli. The establishment of the three-term contingency is a criterion for stimulus control, and can be used to describe complex behavior. Since behavior analytic terms are a vital part of the DDT, some of them will be described in closer detail in the following section.

Reinforcement. We can say that a behavior has been reinforced if the behavior is directly followed by a stimulus, while other stimuli (third variables) have been controlled for and could not interfere and that the behavior later increases in frequency. This stimulus is called a reinforcer, and the process is called reinforcement (Cooper, Heron, & Heward, 2007). A reinforcer also makes the preceding stimulus conditions relevant. Reinforcers are needed both for acquiring new behavior as well as maintaining already learnt behavior. A reinforcer can be either positive or negative, meaning to either add (positive) a stimulus or subtract (negative) a stimulus. The terms positive and negative must by no means be confused with feelings, emotions or similar cognitive states. Reinforcers and the concept of reinforcement are strictly behavioral with clear guidelines on how to interpret them. Again, there should be no confusing reinforcer with reward. Rewards may be intended as motivation, but there is no clear scientific description of how a reward should work altering behavior. A reinforcer, as described, must increase (or maintain) behavior. If there are no signs of increase in behavior, we cannot talk about reinforcement.

Sensory Reinforcement. Sensory reinforcement is discussed by Catania (2013). He claims that lights, sounds and other similar events have been described as neutral in comparison to strong reinforcers or punishers such as food, water or slaps. Though being labeled neutral, any events that are consequences of behavior usually have some kind of effect on the behavior, meaning it's unlikely that they are truly neutral. Catania provides an example where a rat is pressing a lever in darkness leading to the illumination of a light,

describing how lever pressing will increase briefly and thus the light will serve as a weak reinforcer (Catania, 2013). Sensory reinforcers alone are arguably not very potent but can be discussed in relation to curiosity and exploration although the definitions of these phenomena vary.

Extinction. Extinction is another procedure and is defined in relation to reinforcement. When the procedure of reinforcement of behavior stops, the procedure of extinction can start, resulting in a decrease in frequency of that behavior (Cooper et al., 2007). There is no punishment in extinction. Punishment is a procedure of its own and like reinforcement it can be positive (adding) or negative (subtracting). Punishment has the same criteria as reinforcement except that the wanted result is that behavior decreases, much like extinction. Since it is meaningless to talk about extinction without reinforcement, many would argue that extinction should be treated only as the absence of reinforcement. On the other hand we should keep in mind that forgetting and response blocking is not treated as extinction (Cooper et al., 2007). Although no reinforcement is administered in these two examples, the behavior that usually produces the reinforcement is not present either. While a decrease in behavior is the main result of extinction other effects might occur as well. Most notably is the extinction burst, which is an immediate increase in behavior frequency following the withdrawal of reinforcement (Cooper et al., 2007). It is a frequently observed phenomenon but it is short-lived. Another burst may occur later in the procedure, commonly when the behavior has dropped to its low point, called spontaneously recovery. It is also a short-lived effect and will soon disappear if the extinction continues.

Stimulus Control. Stimulus control technically occurs when the frequency of a response is changed in the presence of an antecedent stimulus. If the responses conducted in the presence of a given stimulus produce reinforcement at a higher rate than the responses in the absence of given stimulus, we say that the stimulus acquire control of behavior

(Dinsmoor, 1995a, 1995b). An antecedent stimulus is a stimulus that precedes the behavior and is often referred to as the discriminative stimulus. A discriminative stimulus signals that reinforcement is available for particular responses. By emitting the appropriate behavior in the presence of the discriminative stimulus a reinforcer will be produced. The condition where no discriminative stimulus is present is called stimulus delta (Cooper et al., 2007). Stimulus delta is the name of every other stimulus present that does not signal available reinforcement. By responding in the absence of the discriminative stimulus, no reinforcement will be administered (Cooper et al., 2007). It is worth mentioning that the discriminative stimulus only is effective if the subject can observe it. In other words, it's the consequence that the discriminative stimulus is correlated with rather than its informativeness that determines the reinforcing effectiveness. The history of being reinforced paired with the discriminative stimulus makes the behavior to be under stimulus control.

Example. Rat experiments often take place in a variation of an operant conditioning chamber, also known as a Skinner box, usually containing two or more levers. For rats, responding on levers is maintained as long as reinforcers, usually water or food, are delivered. When reinforcement stops, behavior will decrease over time. The use of the abovementioned terms of reinforcement, extinction and stimulus control in behavior analytic studies can be illustrated by the following experiment of Sagvolden and co-workers (1992).The subjects, the SHR rats, were water deprived, making water a potent reinforcer. During the fixed-interval (FI) condition, ceiling light functioned as the discriminative stimulus, signaling the availability of the reinforcement, the water. During the extinction (EXT) period the ceiling light was off. No discriminative stimulus was therefore present and no water was ever administered. As described earlier, during extinction, responding decreased. The alternation between these two components lets us study stimulus control as the animals should refrain from responding in the EXT component. Stimulus control is

observed when the appropriate responding for each schedule occurs during the corresponding stimulus (Catania, 2013). SHR have frequently been studied on Mult FI EXT schedules. The fixed-interval component in this schedule is an operationalized measure of motor impulsiveness, activity and reactivity to reinforcers. The extinction component in this schedule is an operationalized measure of sustained attention and sensitivity to stimulus change (Sagvolden, 2000)

Spontaneously Hypertensive Rat; Suggested as an Animal Model of ADHD

While the DDT offers a fundamentally unique viewpoint on ADHD, experiments are needed to test this theory and further investigate the disorder. Often, animal models are used to study behavior. Although animal models cannot be used in studies of complex human behavior like language or interaction with others, they can offer insight into activity patterns, stress responses and basic needs such as eating or sleeping. Animal models can also be used to study how different variables affect brain and dopamine activity as well as neurological changes. No animal model completely mimics a human disorder, but they can imitate complex patterns of behavior which mimics the human disorder. By using animal models the disorder can be assessed in a simple system where the environmental control is higher and manipulations or interventions are easier than with complex humans. Although other primates' brains resemble the human brain more so than rodents, rodent models of ADHD have other advantages such as being genetically more homogeneous, they can be easily bred, are less expensive (and less expensive to maintain) and a lot more is known about them in terms of neurobiology (Russell et al., 2005). For good animal models of human mental disorders there are three sets of criteria that must be fulfilled. These are construct validity, face validity and predictive validity (Sagvolden & Johansen, 2012; Sagvolden, Russell, et al., 2005; Willner, 1986). These criteria have been assessed in relation to ADHD as well (Sagvolden, 2000). A good animal model should also share the traits of the human disorder

such as symptoms, etiology and treatment (Sagvolden, Russell, et al., 2005). There are a variety of different animal models trying to mimic the traits of different human diagnosis. This is also true for ADHD, and a wide range of rodent models have been proposed. Sagvolden et al. (2005) mention models that have been exposed to toxins as well as models which have had interference with neurochemical systems, genetic manipulation or rearing in social isolation. Some of the models mentioned are the genetic manipulated Wistar-Kyoto Hyperactive rat, Naples high-excitability rat, DAT-Knockout mouse, Acallosal mouse, and Wig rat, the toxin exposed 6-OHDA-lesioned rat, Polychlorinated Biphenyl-exposed rat and Lead-exposed mouse as well as rats reared in social isolation and rats exposed to interference with neurochemical systems like selective brain lesions, Nucleus Accumbens core lesion *and* Subthalamic lesion (Sagvolden, Russell, et al., 2005). Some of these models such as the Acallosal mouse, WKHA rat, Naples high-excitability rat, lead-exposed mouse and rats reared in social isolation, did not quite satisfy the criteria for animal models of ADHD. The reason these models did not meet the criteria for animal models of ADHD was either due to a focus on symptoms of hyperactivity that was less important and are likely to give limited insight in ADHD research or the models are constructed in a way that could not be related to clinical diagnoses of humans (Sagvolden, Russell, et al., 2005). So, although a variety of different rat and mouse strains exhibit hyperactivity, it is actually few that meet the complete set of criteria for model validation (Russell et al., 2005; Sagvolden & Johansen, 2012). The animal model Spontaneously hypertensive rat (SHR) is the most frequently used model of ADHD (Sagvolden, 2000) in experiments (Johansen et al., 2007; Johansen & Sagvolden, 2004; Johansen et al., 2005; Knardahl & Sagvolden, 1979; Sagvolden, Hendley, et al., 1992; Sagvolden, Metzger, & Sagvolden, 1993; Wickens et al., 2004). The validity of the model has been assessed by Sagvolden (2000) and it has been argued that the SHR gives the best characterization of ADHD, by best fulfilling Willners (1986) validation criteria. This has later

been addressed, and while it's nearly impossible to fulfill all the validation requirements because of the nature of ADHDs description, the conclusion is still the same; the SHR remains the animal model that best fits the criteria for ADHD (Russell et al., 2005; Sagvolden & Johansen, 2012; Sagvolden, Russell, et al., 2005).

SHR: History and Background

The SHR model was bred from Wistar Kyoto rats (WKY) with high blood pressure and hypertension traits (Okamoto & Aoki, 1963) where increased behavior responding and hyperactivity has since been observed. They did this by breeding a male WKY rat with the hypertension trait with a female WKY rat with slightly above average blood pressure. After repeated selective breeding of high blood pressure and spontaneously hypertension, all rats showed stable hypertensive traits in early ages and increased blood pressure as they aged (Okamoto & Aoki, 1963). They named the breed the spontaneously hypertensive rat as they managed to produce a strain with hundred percent occurrence of spontaneously hypertension.

SHR: Main Behavioral Characteristics

SHR show all the main behavior characteristics of ADHD; inattention without any obvious sensory problems (lack of stimulus control), motor control problems, motor impulsiveness and hyperactivity (Sagvolden, 2000; Sagvolden, Russell, et al., 2005). Inattention and hyperactivity is not present in novel situations, but will develop gradually over time (Knardahl & Sagvolden, 1979; Sagvolden, Russell, et al., 2005). SHR also show increased variability in behavior, just as the case is in children with ADHD (Sagvolden, 2000; Sagvolden, Russell, et al., 2005). In general, SHR is more sensitive to delay of reinforcement (Johansen et al., 2005; Sagvolden et al., 2009) with a steepened delay-of-reinforcement gradient (Johansen et al., 2007) like their human ADHD counterparts (Sonuga-Barke et al., 1992). Behavior differences between SHR and WKY have been argued to be due to changed reactivity to reinforcers (Sagvolden, Johansen, et al., 2005; Sagvolden, Metzger, et al., 1993;

Sagvolden, Metzger, et al., 1992). It has been shown that reactivity to reinforcers can be altered with drugs and it has been argued that SHR behavior can be more sensitive towards immediate reinforcement and thus less sensitive to delayed reinforcement when compared to WKY (Sagvolden, Metzger, et al., 1992). In fact, some drugs have been found to virtually normalize SHR behavior (Sagvolden, 2006). Much like children with ADHD, it has been observed that more frequent reinforcement minimizes the differences between control groups and the SHR rats (Sagvolden, Metzger, et al., 1993).

Studies and Findings Related to Stimulus Control and Sensory Reinforcers

Inattention in particular is a prominent deficit in ADHD and is in many studies of SHR operationalized as a lack of stimulus control. The exact causes of this lack of stimulus control are not known, but it is possibly a combination of several factors. Factors contributing to deficit stimulus control may include effects of sensory reinforcers and discrimination problems. In the following section, a selection of SHR studies and their findings will be presented for a closer look on stimulus control in regards to sensory reinforcement and discrimination problems. Included at the end of this section is a study showing that, like observed in SHR, a lack of stimulus control is also found in children with ADHD. This is presented as a validation of SHR as an animal model, and shows that findings in SHR may predict findings in children with ADHD.

Sagvolden, Hendley & Knardahl, 1992. In 1992 Sagvolden and co-workers published an article where they wanted to behaviorally characterize SHR and WKY in comparison to two newly developed strains called WKHT and WKHA (Hendley et al., 1986). They performed a series of tests that had previously been used on WKY and SHR rats and that had produced differences in responding between the two strains. A total of three different tests where used, including a multiple fixed-interval (FI 2-min) extinction (5-min EXT) schedule. A schedule is termed multiple when two (or more) schedule components operate in

alternation in the presence of different stimuli (Catania, 2013). Although Sagvolden and colleagues (1992) wanted to investigate and compare the behavior profiles of four strains of rats, a particularly interesting effect was observed in SHR during the multiple fixed-interval extinction schedule of reinforcement (mult FI EXT). The rats had already been trained to press the installed left lever for water reinforcement. The right lever was present, but was never associated with water reinforcement. Not every lever press produced water, only the first press after two minutes did. In this schedule, light feedback was installed above the levers and would illuminate at every lever press, but it was only active for one lever at a time. No strain differences in responding were found in the response feedback light condition during the fixed-interval part of the schedule and almost no lever presses where observed on the right lever, even when response feedback was scheduled there. In the extinction component on the other hand, the rate of responding in the SHR was about twice as high as in any other strain. Further, by installing the response feedback light above the left lever the response rate of the SHR rose to as much as four times the other strains. Sagvolden and co-workers (1992) concluded the following about the results: "Response feedback may act as sensory reinforcers. Thus, the selective reactivity of SHR to response-produced light feedback stimuli during the extinction component suggests that these stimuli have a much higher reinforcing value in the SHR strain than in any of the three other strains. (…) the present results indicate that the SHR subjects were unable to discriminate between light as response feedback and light signaling delivery of water" (pp.56). Hence, two possible interpretations were described, that the response feedback light worked as a sensory reinforcer and much more so for the SHR than others and that SHR had discrimination problems between light as response feedback and as the signal for reinforcement (light from water tray).

Sagvolden, Pettersen & Larsen, 1993. A study was done by Sagvolden, Pettersen and Larsen (1993) where they partly replicated the study by Sagvolden et al. (1992). In this study they included open field, both free exploration and forced exploration, as well as the Mult FI 2-min EXT 5-min schedule used in the original study. This study included three new strains of rats, Wistar, Sprague-Dawley (SPRD) and PVG (hooded) rats in addition to SHR and WKY. In summary they replicated the original findings with SHR responding as previously shown. Yet again the conclusion was that this could be due to either reinforcing properties of the response feedback light in SHR or discrimination problems in SHR.

Wickens, Macfarlane, Booker & McNaughton, 2004. Inspired by the Mult FI 2-min EXT 5-min schedule used by Sagvolden and co-workers (1992), Wickens, Macfarlane, Booker and McNaughton (2004) tested another rat strain called the New Zealand genetically hypertensive rat (GH) and compared it to its control strain Wistar in addition to the SHR and WKY. They obtained similar results for extinction during the condition where a response feedback light was in effect. However, they did not present any data of lever presses without response feedback light and it is therefore not possible to compare responding with and without response feedback light.

Johansen, Killeen &Sagvolden, 2007. A few years later Johansen and colleagues (2007) did an experiment where they "investigated behavioral variability of non-target responses during acquisition in SHR and WKY controls" (pp.2). In addition to this they wanted to test a way of measuring delay-of-reinforcement gradients in the WKY and SHR. They used a modified operant chamber that they called a hole-box where one wall had 20 holes. These holes were activated as the rats broke the photocell in them with their nose. By performing the target behavior of nose pokes in some of the holes the rats would produce a stimulus in the form of flickering the house light or activating a buzzing sound. The light flickering and the sound were included to test whether the response light and sound feedback

acted as sensory reinforcement as proposed by Sagvolden and co-workers (1992). Johansen and colleagues (2007) results suggest that response variability is higher in SHR than WKY. As suggested in the DDT (Sagvolden, Johansen, et al., 2005), response variability started out higher in the SHR than in the WKY and decreased as they progressed with training, but at a slower rate. They also found supporting evidence for a shorter and steeper delay-of-reinforcement gradient in SHR. However they could not conclude that response feedback light and sound worked as sensory reinforcement. The response pattern suggested that holes with feedback were preferred over neutral holes, but by looking at the first six sessions, layout of the holes may have played a bigger role than its sensory consequences. It was also shown that SHR had more pokes in other holes with about a third being in the target hole, which could imply discrimination problems and not sensory reinforcement effects.

Sagvolden, Aase, Zeiner & Berger, 1998. A study with children was done by Sagvolden, Aase, Zeiner and Berger (1998). They did use a two-component schedule of reinforcement similar to the one used in the above mentioned animal studies. More specifically, they used a multiple fixed-interval (FI 30-sec) extinction (2-min EXT) schedule. 20 grade-school boys were used as subjects including 8 who had been diagnosed with ADHD. Apparatus used was a box painted to look like a clown's face, with the lever being the nose and the mouth working as the tray. The ADHD group made overall more lever presses during FI and more than twice as many lever presses during EXT. During EXT, the ADHD kids responded in bursts while the comparison group had almost no responses. As was true for SHR, it was predicted and shown that ADHD children had a steeper delay-of-reinforcement gradient compared to normal children. It was also shown that hyperactivity and short IRT bursts were not present in the beginning but came later as reinforcers cumulated. Additionally it was shown that ADHD children had poor stimulus control during EXT (Sagvolden et al., 1998).

Summary and Conclusions

The DDT (Sagvolden, Johansen, et al., 2005) suggest that ADHD symptoms are caused by altered reinforcement of novel behavior and deficient extinction processes. This is supported by experiments on children with ADHD (Aase et al., 2006; Aase & Sagvolden, 2005; Sagvolden et al., 1998) and SHR (Johansen et al., 2007; Johansen & Sagvolden, 2004, 2005; Johansen et al., 2005; Sagvolden, Metzger, et al., 1993). A frequent responding (hyperactivity), bursts of responses with short IRT's (impulsiveness) and deficient in stimulus control (inattention) has been observed in ADHD (Sagvolden et al., 1998) as well as increased behavior variability (Johansen et al., 2007). One of the prominent deficits in ADHD is inattention, or a lack of stimulus control. Stimulus control is acquired and maintained by reinforcing responses in the presence of a discriminative stimulus, but not in the absence of it. Because of the short delay gradient in ADHD, the relation between the reinforcer and the response will not be contingent when the delay is too long. A multiple fixed interval extinction schedule of reinforcement has been used to test animals and humans with ADHD. The fixed-interval component in this schedule measures motor impulsiveness, activity and reactivity to reinforcers. The extinction component in this schedule measures sustained attention and sensitivity to stimulus change (Sagvolden, 2000). In several studies (Sagvolden, Hendley, et al., 1992; Sagvolden, Pettersen, et al., 1993; Wickens et al., 2004) a response feedback light was added to the Mult FI EXT schedule of reinforcement. Results show an increase in responses for SHR after the implementation of the response feedback light, but it is still unclear why. Specifically, it was only during extinction, and only on the lever that would produce reinforcers (left lever) that the phenomenon occurred. It has been argued that the cause may simply be because the response feedback light serves as a sensory reinforcer. On the other hand, sensory reinforcement is said to usually be weak (Catania, 2013) and reinforcing properties have not been found in later studies (Johansen et al., 2007). Studies

have shown discrimination problems in SHR during extinction. However, there seem to be an additional reinforcing effect of the response feedback light producing the additional increase in responding compared to extinction without response feedback light. Sagvolden and co-workers (1992) suggested that SHR might have trouble discriminating between light as response feedback and light signaling delivery of water (tray light). It can be added that there might also have been discrimination problems between light as response feedback and light signaling availability of a reinforcer (discriminative stimulus, house light). One way to check for this in future studies would be to train rats on a similar condition without the possibility for a conditioning of response feedback light with any other light stimuli. It has been observed that overactivity and impulsiveness is not present in novel situations (Sagvolden & Sergeant, 1998), but a small change in conditions, like installing a response feedback light, might not count as a novel situation but can rather stimulate ‘curiosity’ and ‘exploration’ as effects of sensory reinforcement. More thorough investigations into the matter, why response feedback light leads to increase in behavior, may provide new insights on behavior processes underlying the development of ADHD-like symptoms. If it turns out to be reinforcing properties in the response feedback light, it would shed new light on stimulus control in SHR. Overall this may lead to a better understanding of SHR as an animal model and in turn predictions in ADHD. Further, knowledge on stimulus control may help reduce unwanted behavior variability and behavior of low performance. This may help harness the development of symptoms for ADHD and might have implications for arrangement of treatment or behavior modifying interventions.

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a prevalence of around 2.5% in adults and 5% in children. The dynamic developmental theory suggests that ADHD symptoms are caused by altered reinforcement of novel behavior and deficient extinction of previously learned behavior. Deficit stimulus control or effects of sensory reinforcement may lead to symptoms of ADHD, especially inattention and hyperactivity. The purpose of the present experiment was to investigate the increased response rate observed in SHR/NCrl, an animal model of ADHD, during extinction with the response feedback light, and test whether this activity increase is caused by effects of sensory reinforcement or general discrimination problems. Method: 8 SHR/NCrl and 8 WKY/NHsd were tested on a multiple fixed-interval extinction schedule with response feedback on lever press. Rats were randomized in two groups and trained on different conditions, one with house light as the discriminative stimuli and one with a sound as the discriminative stimuli. Thereafter the conditions were switched in the two groups. Results: The SHR had a generally higher number of lever presses compared to WKY throughout the experiment, and response patterns differed except for FI. Response feedback light produced a similar pattern as in earlier studies, but with some important deviations compared to previous results, whereas stimulus control was not established during the sound feedback condition. Discussion: In conclusion, we found that SHR responding does differ from WKY, validating SHR as an animal model of ADHD. The present study was not an exact replication, and the findings deviated from the findings in the original study which points to procedural differences. The results are discussed in light of differences in the overall procedure like number of different tests and number of sessions as well as specific differences in testing like different water pump.

Keywords: ADHD, SHR, Response feedback light, Stimulus control, Mult FI EXT

Effects of Response Feedback Light: Behavioral Differences Between the Spontaneously Hypertensive Rat (SHR) and Controls

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a prevalence of around 2.5% in adults and 5% in children, with a gender distribution twice as high in boys than girls and 1.6:1 in men:women (American Psychiatric Association, 2013). ADHD can be found all over the world (Faraone, Sergeant, Gillberg, & Biederman, 2003) and is characterized by patterns of behavior that can be observed in multiple settings ranging from home, school and work to interaction with friends and family and other social settings negatively impacting educational and/or social performance as well as performance in work related tasks. The diagnostic and statistical manual of mental disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) features two categories of symptoms for ADHD with a total of nine symptoms for inattention and nine symptoms for impulsiveness/hyperactivity. To fulfill the criteria of having ADHD with a predominant presentation, children must have shown persisting presence of at least six symptoms from either category for at least six months. For adults (over 17 years of age) at least five of the symptoms must have been observed throughout the six months or longer. It is also possible to have a combined presentation by showing six or more (five for adults) symptoms from each category (American Psychiatric Association, 2013). It has been argued that having a combined presentation might be more severe than a predominant presentation (Faraone, Biederman, Weber, & Russell, 1998). When compared to others, people with inattention may have trouble with focusing on details and instructions for tasks as well as organizing tasks or remembering during daily activities (American Psychiatric Association, 2013), especially in situations where stimuli are widely spread over time or other stimuli/sensations (e.g. visual or sound) might be available (Taylor, 1998). Impulsiveness and hyperactivity is generally not prominent in novel situations (Sagvolden & Sergeant, 1998), but will be more pronounced as

the person interacts and gets familiar with the surroundings (Aase & Johansen, 2010). Impulsiveness can be described as the urge of acting without planning ahead (Johansen, Aase, Meyer, & Sagvolden, 2002) which may potentially lead to risky situations with increased chance of low performance behavior and accidents (Taylor, 1998). Hyperactivity can be described as having a much higher activity level or performing activity to an extend not suitable for the situation as well as a high rate of switching between tasks and a general 'restlessness' (Taylor, 1998). The DSM does also state that pattern of symptoms consisting of inattention, impulsiveness and hyperactivity leads to the diagnoses ADHD only if it is not better explained by other disorders like mood, personality or anxiety disorders (American Psychiatric Association, 2013). However, it does not provide an explanation or theory of mechanisms underlying the development of the symptoms in regards to cases including psychosocial problems, reduction of senses or medical complications. A theory was proposed by Sagvolden and colleagues (2005) called the dynamic developmental theory of attention-deficit/hyperactivity disorder (DDT) which embraces these factors and emphasizes the fact that behavior can be formed in a way that may intensify or produce ADHD-like symptoms. The theory is based on behavior analysis and neurobiology and points to two major underlying behavioral processes – altered reinforcement of novel behavior and deficient extinction of previously learned behavior (Sagvolden, Johansen, et al., 2005). The DDT suggests that a hypofunctioning dopamine system may affect these learning mechanisms by creating a shorter window for associating behavior with preceding stimuli and consequences, a steeper and shorter delay-of-reinforcement gradient, as well as a slower extinction of inefficient responses. Because of the short delay gradient in ADHD, when delays are too long the relation between a response and a reinforcer is not contingent and stimulus control may not be established. A lack of stimulus control can therefore explain the attention problems observed in ADHD. Although it is not explicitly mentioned by the DDT, another factor that

may impact inattention (and hyperactivity) is potential effects of sensory reinforcement. To support theories like the DDT, experiments are needed. A valuable and commonly used method for studying behavior patterns, reactions and symptoms are by the use of animal models. There is no animal model that completely mimics all the traits of a disorder, but it is possible to test how different variables can affect both behavior and dopamine activity. A good animal model must fulfill three sets of criteria - face validity, construct validity and predictive validity (Sagvolden & Johansen, 2012; Sagvolden, Russell, Aase, Johansen, & Farshbaf, 2005; Willner, 1986) and it should share similar traits with the human disorder like symptoms, etiology and treatment (Sagvolden, Russell, et al., 2005). The same criteria applies to animal models of ADHD (Sagvolden, 2000). Several rodent models have been proposed for ADHD, but not all of them satisfy the validation criteria (Sagvolden, Russell, et al., 2005). The most frequently used rodent model of ADHD is the spontaneously hypertensive rat (SHR) (Sagvolden, 2000), which was bred from the Wistar Kyoto Rat (WKY) (Okamoto & Aoki, 1963), and it is possibly also the best validated animal model of ADHD (Russell, Sagvolden, & Johansen, 2005; Sagvolden & Johansen, 2012; Sagvolden, Russell, et al., 2005). One study of ADHD using the SHR was done by Sagvolden, Hendley and Knardahl (1992). Their original goal was to behaviorally characterize two newly developed strains, WKHT and WKHA (Hendley, Wessel, & Van Houten, 1986), in comparison to the WKY and the SHR, by using a series of tests that had previously been used for testing the WKY and SHR and had produced strain differences. Amongst the tests used was a multiple fixed-interval (FI 2-min) extinction (5-min EXT) schedule of reinforcement (mult FI EXT) with response feedback light alternating between the left and right lever. Water reinforcement was always associated with lever presses on the left lever. The response feedback light had very little effect during fixed-interval responding. During EXT the rate of responding in SHR was about twice as high as in any other strain, but by installing the

response feedback light (on the left lever) the response rate went up to around four times the other strains. In response to this, Sagvolden, Hendley and Knardahl (1992) made two possible interpretations; "Response feedback stimuli may act as sensory reinforcers. Thus, the selective reactivity of SHR to response-produced light feedback stimuli during the extinction component suggests that these stimuli have a much higher reinforcing value in the SHR strain than in any of the three other strains." and "(…) the present results indicate that the SHR subjects were unable to discriminate between light as response feedback and light signaling delivery of water" (pp.56). These interpretations were done, despite the fact that sensory reinforcement generally is considered having weak reinforcing effects (Catania, 2013) and that no discrimination deficit in SHR relative to WKY had previously been found (Knardahl & Karlsen, 1984). Similar results have been found in later studies (Sagvolden, Pettersen, & C., 1993; Wickens, Macfarlane, Booker, & McNaughton, 2004). The present study is a partial replication of the study done by Sagvolden and co-workers (1992) with emphasis on the mult FI EXT schedule of reinforcement. The purpose of the present experiment was to further investigate the increased response rate observed in SHR during extinction with the response feedback light, and to test whether this activity increase is caused by effects of sensory reinforcement or general discrimination problems.

Method

Subjects

The subjects in this study were a total of 16 rats, 8 SHR/NCrl and 8 WKY/NHsd. The WKY rats were obtained from Harlan UK while the SHR came from Charles River Germany, and all rats were three weeks of age at the time of arrival. They were housed two and two upon arrival in transparent home cages 41 cm x 25 cm x 25 cm (height) and kept in a rack holding up to 16 home cages at the University of Oslo, Domus Medica. After a week of training they were housed individually in white plastic boxes which would now function as

their home cage. All rats were identified by a color and a roman number code on the tip of their tail, made by a marker. The group of 16 was randomized into subgroups to control for possible sequence effects, with four WKY and four SHR distributed across the two subgroups. One group would start with having ceiling light as the discriminative stimulus (Light-Sound-group) and the other would start with a looping sound as the discriminative stimulus (Sound-Light-group). For the Sound-Light-group, light signaling availability of a reinforcer (tray light) would be off during pretraining and testing. A 22h drinking water deprivation schedule was used throughout the experiment. Access to water in the home cage was limited to one hour immediately following each session. Food was accessible in the home cage at all hours. Light was on between 0800 and 2000 and temperature in the housing area was ~22°C. Testing was done on the same hours each day and all rats were experimentally naïve at the start of the experiment. The study was conducted in accordance with the laws and regulations controlling experiments/procedures in live animals in Norway and was approved by the Norwegian Animal Research Authority (NARA).

Apparatus

Four identical standard Campden (410-R) operant champers were used to train and test the animals. The floor was made of small metal bars and the walls were made of metal, with the door being composed of transparent plastic. The four chambers each had two retractable levers installed on each side, above the water tray. There was one 2.8-W white cue light positioned above each lever illuminated by lever press on the corresponding lever (e.g. left light activated by left lever presses). There was a 2.8-W cue light installed in the water tray, illuminated for three seconds every time a reinforcer was available. A small transparent plastic swinging door separated the water hopper from the main room. The water pump was peristaltic, i.e. the water droplet would stay in the cup until it was collected by the animal. There was one 2.8-W house light close to the center of the chamber ceiling. Installed in the

roof of the chambers was a speaker used to make the sound which functioned as a discriminative stimulus during parts of the experiment.

Procedure

Pretraining. The rats had two days of 20 minutes habituation in the operant chambers, before being introduced to the 22h water deprivation (Table 1). The animals were then magazine trained on a variable time (VT) 20 s schedule, delivering drops of water on the average every 20 s independently of the animal's behavior, with a variation range of 20 (VT20/20), for 30 minutes with the tray door open. Then they were trained to open the tray door on a continuous reinforcement schedule, CRF, delivering reinforcers every time the door was opened. In the beginning small droplets of water was placed on the door to help the rats investigating the door. The CRF was run for three sessions. One group of rats, the Sound-Light-group did not have tray light illuminate during water reinforcement. This was done to exclude the possibility that this group could pair tray light with response feedback light. After the initial training, response shaping on the right lever was initiated and postponed, due to the fact that none of the rats were sufficiently magazine trained. Two new sessions of magazine training were conducted, first VT40/30 and then VT20/20. Finally, response shaping was introduced as the rats were trained to press the left lever to activate water reinforcement. The right lever was withdrawn during response shaping. Again, as previously, small droplets of water were used to encourage behavior, this time placed on top of the lever. The final initial training session consisted of CRF with presses on the left lever, which lasted for 30 minutes. The rats were then introduced to two sessions of multiple fixed interval 60s 5-min extinction (Mult FI 60s EXT 300s) schedule, where the first lever press after 60 seconds had elapsed produced a reinforcer. Two sessions of Mult FI 120s EXT 5-min were initiated but terminated due to computer program malfunction. Data from these sessions were excluded

from further analyses. During the training and testing period water was given to the animals ad lib for 1 hour after each session.

Multiple FI-EXT. The schedule used both in the original study, and in this replication was a multiple fixed-interval extinction schedule of reinforcement (Mult FI EXT). Mult FI EXT is a two component multiple schedule and is termed multiple because two (or more) schedule components operate in alternation in the presence of different stimuli, as described by Sagvolden et al. (1992). The following schedule was used for half the rats, the Light-Sound-group. During the fixed-interval 2-min (FI 2-min) schedule component the houselight was on, while during the extinction component (EXT) the houselight was off. In the FI 2-min component, after every 2-min interval had elapsed, the first lever press was reinforced by a droplet of water. Water reinforcement was always associated with responses on the left lever, never on the right lever. Whenever the reinforcer was available, the cubicle where the water was delivered was lit up by a light, lasting approximately three seconds. Contrary to the original study, where the water droplet was available only for the three seconds the light was lit, the water droplet in this replication study would remain available until the rat collected it, which in turn potentially could lead to multiple droplets accumulating. If the rat didn't drink the water given in the FI, it would remain available in the extinction component, but there was no water ever administered in this component. Every session was split into four parts alternating between two FI 2-min components, with the same properties, and two 5-min EXT components in the sequence FI 1 (FI 120-sec intervals) – EXT 1 (300-sec) – FI 2 (FI 120-sec intervals) – EXT 2 (300-sec). For the FI 2-min components a maximum delivery of seven reinforcers where administered and the total duration was maximum 15 minutes ending with the termination of a FI (but not necessarily a reinforcer as in the original study). The EXT components lasted 5 minutes with the second EXT component ending the session. During half the sessions, the first and third week of

testing, the light above the right lever was lit for the duration of the press on this lever (Table 1). This is called the response feedback condition. During the other half of the sessions, the second and fourth week of testing, the light above the left lever was lit for the duration of the press on this lever. Light was never lit above both levers at the same time. In the other half of the rats, the Sound-Light-group, we ran a similar schedule of multiple fixed-interval extinction schedule of reinforcement. This was the group that had never been exposed to tray light during training. The difference between this schedule and the original is that the house light was on during both the FI 2-min components and the 5-min extinction components but would not function as a discriminative stimulus. What worked as the discriminative stimulus in this schedule was a looping sound that would last the entire FI 2-min component. There was no sound during EXT. In addition, no tray light would get lit during delivery of water. Again, feedback light started on the right lever, then alternating each week between right and left for four week of testing. When the experiment had been run for four weeks, alternating two weeks with response feedback on right lever and two weeks on left lever, the two groups (Light-Sound and Sound-Light) switched stimulus conditions. The eight rats starting with house light as discriminative stimulus would now run with sound as discriminative stimulus while the eight rats starting with sound as discriminative stimulus now had house light as discriminative stimulus. The switch was done so that we would have a total of eight SHR and eight WKY observations on both the replication condition and the new condition while controlling for sequential effects. With this setup we could also strengthen the research design and have sufficient statistical power to detect potential effects.

Data Collection

Data were recorded by a computer linked to the operant cages. The program used was developed by Prof. Per Holth through Visual Basics (Microsoft, Released 2010). The program recorded every press on the left and right lever as well as tray visits, and displayed it

as a graph on the computer. The text files produced by this program showed strings of numbers that coded for both left and right lever presses, tray visits, whenever the feedback light was lit above the right and left lever as well as the whenever the ceiling light and sound was activated. In these strings 15 lines equaled 1 second. Visual Basics (Microsoft, Released 2010) was used to make a code that could read these text files and turn the strings into a readable format for other computer programs. A mix of the Visual Basics code and manual counting was used to read and validate the data and transfer them to make Microsoft Excel files. Data from the Excel files were transferred to SPSS (IBMCorp, Released 2011) for early analysis. The final SPSS files were double-checked against some of the original numbers to ensure that the data were correct. The files were then exported to Statistica (StatSoft, Released 2013) for statistical analyses.

Data Analysis

The analyses were based on the results obtained during sessions 15 through 70. The FI 2-min components were divided into 12 consecutive 10-sec segments while the EXT components were recorded as 30 consecutive 10-sec segments, but later merged into 5 consecutive 1 min segments. Data for tray visits were recorded but are not presented. All statistical analyses were done in Statistica 12.0 (StatSoft, Released 2013). Data were evaluated by multivariate analyses using Wilks lambda (MANOVA's) when the degree of freedom relative to the number of levels of the repeated factor permitted this approach, or by univariate analyses of variance (ANOVAs). Statistica allows a maximum of 150 independent variables to be entered into one analysis. For this reason, and to simplify the interpretation of effects, the number of independent variables was limited the following way: for FI we merged data into 2 levels of Feedback (on right and left lever), 2 levels for FI-component (within session FI 1 and FI 2), 2 levels for Week (feedback left first week; feedback right first week; feedback left second week; feedback right second week),1 level for FI-intervals (2-5

together) and 12 levels for Segment. For EXT we merged data to receive 2 levels for Feedback (on right and left lever), 2 levels for EXT-component (within session EXT 1 and EXT 2), Week (feedback left first week; feedback right first week; feedback left second week; feedback right second week) and 5 levels for Segment. Because some of the rats were stationary in the beginning of FI and some rats didn't finish all seven rounds of FI within a single FI component, the first and the two last FI intervals were excluded from analyses. In order to limit the number of variables, the average for FI 2-5 was used, and data for the two feedback sequences (Light-Sound and Sound-Light) were combined and analyzed in regards to SHR and WKY, but not in regards to their sequential order.

Results

The SHR had a generally higher number of lever presses compared to WKY throughout the experiment, but the response pattern was similar. Results are presented for the two conditions of light as discriminative stimuli and sound as discriminative stimuli.

Fixed-interval responding

Light: At a descriptive level, for both SHR and WKY rats, a general increase in responses was seen over the course of the four weeks in FI, with the second FI component having slightly less responses than the first (Figure 1). The statistical analyses showed that in general, SHR emitted more lever presses than WKY as reflected by a statistically significant main effect of strain, $F(1,14 = 6.22; p < 0.05)$. The analyses showed a significant main effect of FI component $F(1,14 = 68.05; p < 0.001)$ with more lever presses in FI 1 compared to FI 2. There was also a statistically significant main effect of segments $F(11,4 = 191.96; p < 0.001)$ with a general increase in responses across segments. The analysis showed statistically significant group x feedback x FI-component $F(1,14 = 6.70; p < 0.05)$, and week x segment $F(11,4 = 27.60; p < 0.01)$, interaction effects as well as an FI-component x segment $F(11,4 = 16.74; p < 0.01)$ interaction effect.

Sound: At a descriptive level, a general increase can be seen over the course of the four test weeks (Figure 3) for both strains. In FI-component 1, more lever presses can be observed compared to FI-component 2. The statistical analyses showed a group difference between SHR and WKY. Overall more lever presses was produced in FI-component 1 compared to FI-component 2 by both strains. The analysis showed a statistically significant main effect of group $F(1,14 = 14.64; p < 0.001)$, and FI-component $F(1,14 = 74.47; p < 0.001)$. The analysis also showed a statistically significant main effect of segment $F(11,4 = 40.78; p < 0.01)$. The following statistically significant interaction effects was shown in the analysis: week x segment $F(11,4 = 138.81; p < 0.001)$, week x FI-component $F(1,14 = 0.73; p < 0.05)$, group x week x segment $F(11,4 = 85.37; p < 0.001)$, FI-component x segment $F(11,4 = 8.76; p < 0.05)$, week x segment x feedback $F(11,4 = 20.39; p < 0.01)$, week x FI-component x segment $F(11,4 = 16.52; p < 0.001)$ and group x week x FI-component x segment x feedback $F(11,4 = 6.09; p < 0.05)$

Responding During Extinction

Light: At a descriptive level; over the course of the four weeks, a similar number of responses were observed in EXT-component 1for WKY rats whereas EXT-component 2 showed a decrease (Figure 2). For SHR, a higher number of lever presses was observed in EXT-component 1 during weeks with response feedback light with the exception of the first week (Figure 5). During EXT-component 2 a decrease in responding is observed both over segments (Figure 2) and over weeks (Figure 5). The statistical analyses showed that more lever presses was generally emitted by the SHR compared to the WKY as reflected by a statistically significant main effect of strain, $F(1,14 = 16.47; p< 0.01)$. Responding decreased across the two EXT-components in both strains, but more so in SHR as compared to WKY. Fewer lever presses were observed in EXT-component 2 as compared to EXT-component 1, and the analyses showed a statistically significant main effect of EXT-component, $F(1,14 =$

40.11; p< 0.001), and a significant group x EXT-component $F(1,14 = 5.17; p < 0.05)$, interaction effect. The analysis also showed a statistically significant main effect of segment $F(4,11 = 15.51; p < 0.001)$ as well as statistically significant interaction effects for group x segment $F(4,11 = 6.85; p < 0.01)$, week x feedback $F(1,14 = 6.66; p < 0.05)$, group x week x feedback $F(1,14 = 8.19; p < 0.05)$, feedback x EXT-component $F(1,14 = 50.93; p < 0.001)$, group x feedback x EXT-component $F(1,14 = 29.97; p < 0.001)$, week x EXT-component $F(1,14 = 5.60; p < 0.05)$, feedback x segment $F(4,11 = 17.43; p < 0.001)$, group x feedback x segment $F(4,11 = 11.10; p < 0.001)$, week x segment $F(4,11 = 10.53; p < 0.001)$, group x week x segment $F(4,11 = 4.21; p < 0.05)$, EXT-component x segment $F(4,11 = 8.72; p < 0.01)$, group x EXT-component x segment $F(4,11 = 3.95; p < 0.05)$, feedback x EXT-component x segment $F(4,11 = 3.38; p < 0.05)$ and feedback x week x EXT-component x segment $F(4,11 = 8,66 < 0.01)$.

Sound: At a descriptive level, WKY had a generally lower response pattern than SHR (Figure 4) with the number of SHR responses at around 3-4 times that of WKY. SHR showed an increase in responses over the duration of the four test weeks for EXT-component 1. For EXT-component 2, SHR showed a decrease in responses over segments, but the number of responses was flat (Figure 6). WKY showed a flat response patters for both EXT-components over the course of the four weeks. The statistical analysis showed a statistically significant main effect of group $F(1,14 = 10.40; p < 0.01)$, week $F(1,14 = 4.83; p < 0.05)$, EXT-component $F(1,14 = 27.12; p < 0.001)$, segment $F(4,11 = 18.74; p < 0.001)$ and feedback $F(1,14 = 6.06; p < 0.05)$. In addition, analysis show a statistically significant interaction effect of group x EXT-component $F(1,14 = 7.55; p < 0.05)$, group x segment $F(4,11 = 4.54; p < 0.05)$, week x segment $F(4,11 = 4.98; p < 0.05)$, group x feedback $F(1,14 = 6.99; p < 0.05)$, feedback x EXT-component $F(1,14 = 7.54; p < 0.05)$, week x EXT-component $F(1,14 = 6.03; p < 0.05)$, feedback x segment $F(4,11 = 3.37; p < 0.05)$, EXT-component x segment $F(4,11 =$

12.17; $p < 0.001$), and group x feedback x EXT-component x segment $F(4,11 = 3.73; p < 0.05)$.

Responses on the Right Lever

The total number of responses was zero or very close to zero both during the fixed-interval conditions and extinction. There were very small and negligible differences both between SHR and WKY and between light and sound conditions in responses on the right lever. Hence, data for this lever is not presented.

Discussion

The purpose of the present experiment was to further investigate the increased response rate observed in SHR during extinction with the response feedback light, and test whether this activity increase is caused by effects of sensory reinforcement or general discrimination problems. The present study was not able to replicate the findings in the original study. The present data show that SHR were more active than WKY during FI with Light as discriminative stimulus, having a steeper fixed-interval scallop, with responses accelerating towards the end of the interval (Figure 1). More responses and a steeper scallop were observed for both strains during FI-component 1 compared to FI-component 2. During EXT, SHR emitted more responses than WKY but the overall number of lever presses was lower than during FI (Figure 2). A large difference was shown when comparing EXT-component 1 to EXT-component 2 for both strains. This might indicate a within session learning or an overall higher stimulus control in respect to EXT-component 2, but not EXT-component 1. Responding with Sound as discriminative stimulus showed a similar pattern for FI as with Light (Figure 3). During EXT for the Sound condition, no stimulus control was observed for either strain (Figure 4) and the number of responses was higher than in the Light condition. This might indicate that it is more difficult to establish sound as a discriminative stimulus or it may be linked to the procedure or the equipment used in this study. In addition,

during this condition (Sound) the light signaling the delivery of a reinforcer (tray light) was never turned on. This was done to exclude the possibility of a pairing between the tray light and the response feedback light, but it may have had the effect that the rats never learned when reinforcement was available. Still, SHR showed a higher response rate compared to WKY during this condition. Interestingly, a decrease in responses was observed in EXT-component 2 compared to component 1and also over segments within EXT-component 2 for both strains (Figure 4) as in the Light condition. Given the lack of stimulus control, it is difficult to consider this a within session learning effect.

During EXT in the Light condition, the behavioral pattern obtained in the present study is different from the pattern found in earlier studies (Sagvolden et al., 1992; Sagvolden, Pettersen, & Larsen, 1993) were large strain differences with and without the inclusion of a response feedback light on the left lever, was observed. As previously described, EXT-component 2 had a generally lower number of responses and a different pattern then EXT-component 1 (Figure 5). When we only focus on data from EXT-component 1, the behavioral pattern is more similar to the data in the original study. The most obvious difference in the present findings compared to earlier findings are seen during the first week of testing where a higher number of emitted responses was observed compared to the other weeks. This difference might be the result of a different learning history in rats from the original study compared to this partial replication. In Sagvolden and co-workers (1992) study the rats had completed several other tests before entering the mult FI EXT schedule of reinforcement test, including open field tests, both forced exploration and free exploration (27 sessions) and it is a possibility that rats used in the present study needed longer time to establish stimulus control. Since the original study included several other tests in addition to the mult FI EXT and there is limited space in the article, some variables might not have been described well enough for an actual replication. Additionally other differences in the procedures may have

had an effect on data. For instance, the delivery of water reinforcers differed between the two studies. While Sagvolden and colleagues (1992) study delivered reinforcers by a lever that was lowered after 3 seconds, the present study used a peristaltic pump. This may have led to the rats 'saving' water or more probably finding the water independent of lever presses. A difference in number of test sessions may also have contributed to the differences in data. In the original paper, there was no explanation for the high and the uneven number of sessions for each condition. Both due to limited time and to strengthen the research design, an even, lower number of sessions were chosen in present study. Seen in retrospective of present study, the explanation for the number of sessions in Sagvolden and co-workers (1992) study may have been to stabilize lever pressing, as it may have taken longer to establish stimulus control than the number of sessions used. Besides the differences for week 1 (Figure 5) when comparing patterns across studies, the remaining pattern is similar. In present study, there seem to be effects of response feedback light, but the effect is not as large as in previous experiments. There is a distinct difference when comparing SHR and WKY, and this is supporting the validity of SHR as an animal model of ADHD. By including the Sound condition we wanted to exclude the possibility of the rats pairing response feedback light with light from the water tray or house light (discriminative stimulus). If the same pattern had been observed in this condition as in the Light condition, it could have supported conclusions that largely exclude problems with discriminations and conditioning of the response feedback light as possible explanations for the lack of stimulus control in SHR during extinction. Further, it would have strengthened the interpretation that the effect of response feedback light is linked to sensory reinforcement. Unfortunately, since it was not established any form of stimulus control in the Sound condition (EXT), no such comparison can be done. Another supporting argument for response feedback light acting as sensory reinforcement would be if we could observe a distinct increase in responding on the right lever when response feedback

was scheduled for presses on this lever. Results show that almost no lever presses was observed on the right lever regardless of feedback-condition and thus, no support for response feedback light as sensory reinforcement can be found (in regards to this hypothesis). In general, it is possible that light feedback can act as a sensory reinforcer, but in the present study, the low number of responses on the right lever, even during response feedback, may have been produced by competition with the larger water reinforcer produced by responses on the left lever, with the latter reinforcer controlling behavior. The interpretation that feedback light does not act as a sensory reinforcer is supported by previous studies (Johansen, Killeen, & Sagvolden, 2007).

In conclusion, we found that SHR responding does differ from WKY, both during FI and during EXT validating SHR as an animal model of ADHD. The present study was not an exact replication, and the findings deviated from the findings in the original study which points to procedural differences. In addition, the extra condition of Sound included to investigate effects of response feedback light and possible discrimination problems with other light stimuli in the test chamber was inconclusive as no form of stimulus control was established in this condition. This study was not able to satisfactory investigate why response feedback light have an impact on SHR during EXT nor find out more about the discrimination problems in SHR. Hence, a firm conclusion about why response feedback light has an impact on SHR during EXT cannot be drawn based on the findings in the present study. More studies are needed on stimulus control in SHR, and should investigate the strength of sensory reinforcement in this strain. The ultimate goal is of course to increase the knowledge and understanding of the human diagnoses, in this case ADHD. Findings from studies of sensory reinforcement and variables affecting stimulus control may have implications for the understanding and treatment of ADHD. Given that sensory reinforcement has an additional effect to more potent reinforcers or during periods of no reinforcements

(extinctions), it may help children focus on the wanted behavior while restricting variability. More knowledge about stimulus control may also help restricting variability and overactivity which may be disruptive for themselves or others. Since people with ADHD generally are delay minimizers or delay aversive, trying to reduce overall delay instead of maximizing profit (Sonuga-Barke, Taylor, Sembi, & Smith, 1992), establishing stimulus control over behavior to help them wait for more potent reinforcers may prevent situations where risk-taking and low performance behavior is involved. The field of ADHD is ever expanding and further studies are required for a better understanding of stimulus control in SHR and possible sensory reinforcing effects. Studies on stimulus control in an animal model may increase the understanding of symptoms and behavior changes observed in children with ADHD.

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Table 1

EXPERIMENTAL PROCEDURE

Session Number	Behavior procedure	Notes
1-2 [2]	20-min habituation	For operant chambers
No training		Starting deprivation 12.30
3 [1]	30-min magazine training, VT20/20	
4-6 [3]	30-min magazine training, CRF	
7 [1]	2 x 30-min magazine training, VT40/30	Shaping right lever was scheduled and terminated
8 [1]	30-min magazine training, VT 20/20	
9 [1]	Response shaping	Left lever installed
10 [1]	30-min CRF, left lever	
11-12 [2]	Multiple fixed-interval (60-sec) extinction (5-min)	(Mult FI EXT)
13-14 [2]	Mult FI EXT 120-sec, 5-min	Terminated
15-21 [7]	Mult FI EXT 120-sec, 5-min	Response feedback right lever
22-28 [7]	Mult FI EXT 120-sec, 5-min	Response feedback left lever
29-35 [7]	Mult FI EXT 120-sec, 5-min	Response feedback right lever
36-42 [7]	Mult FI EXT 120-sec, 5-min	Response feedback left lever Conditions switched
43-49 [7]	Mult FI EXT 120-sec, 5-min	Response feedback right lever
50-56 [7]	Mult FI EXT 120-sec, 5-min	Response feedback left lever
57-63 [7]	Mult FI EXT 120-sec, 5-min	Response feedback right lever
64-70 [7]	Mult FI EXT 120-sec, 5-min	Response feedback left lever

Figure 1

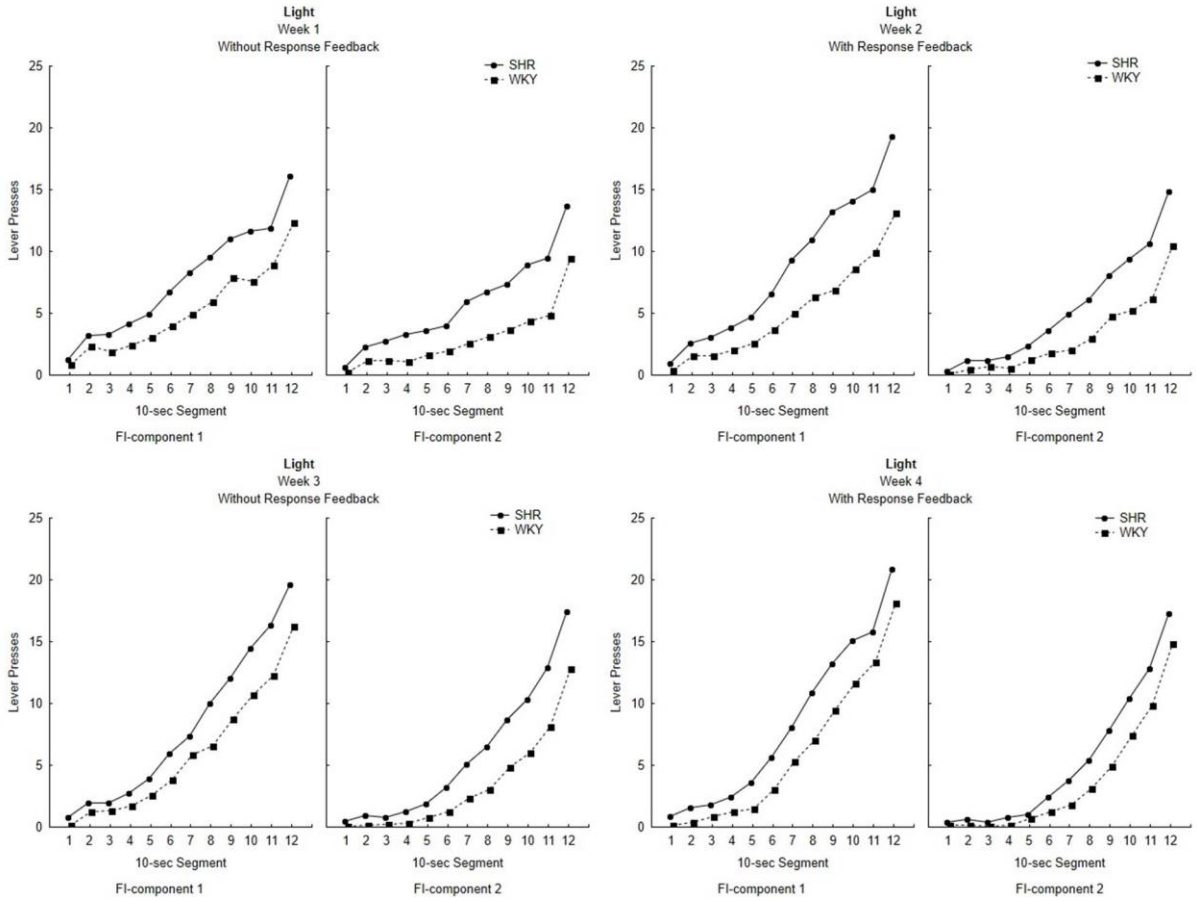

Figure 2

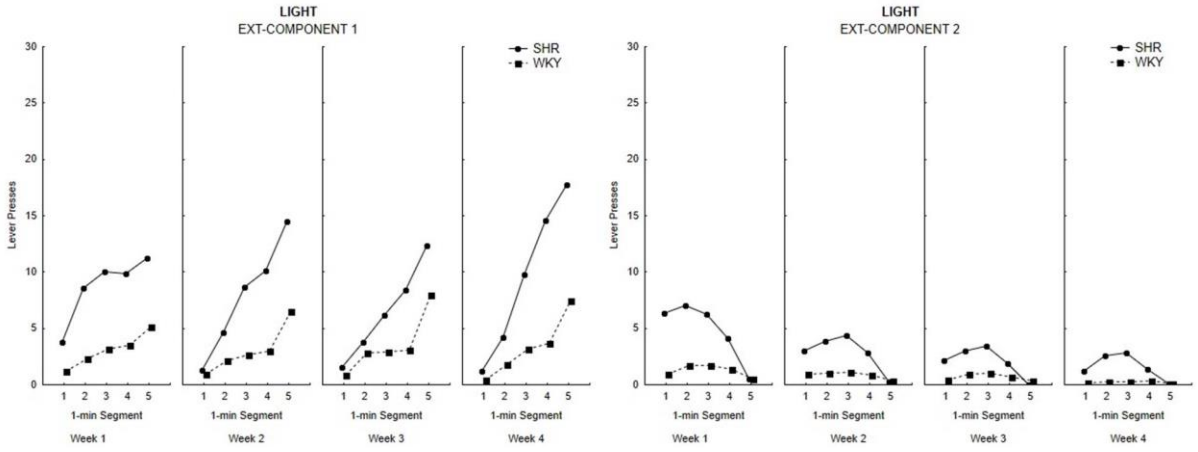

Figure 3

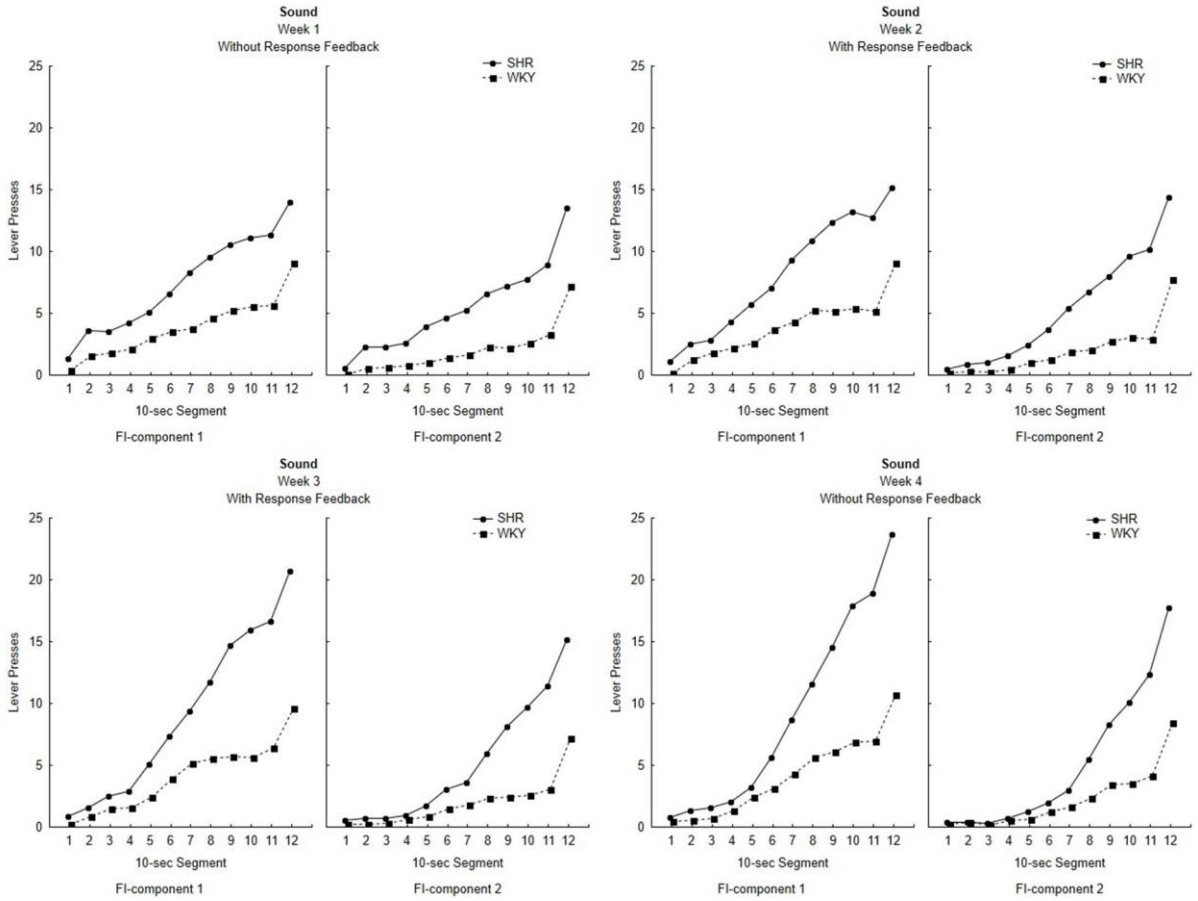

Figure 4

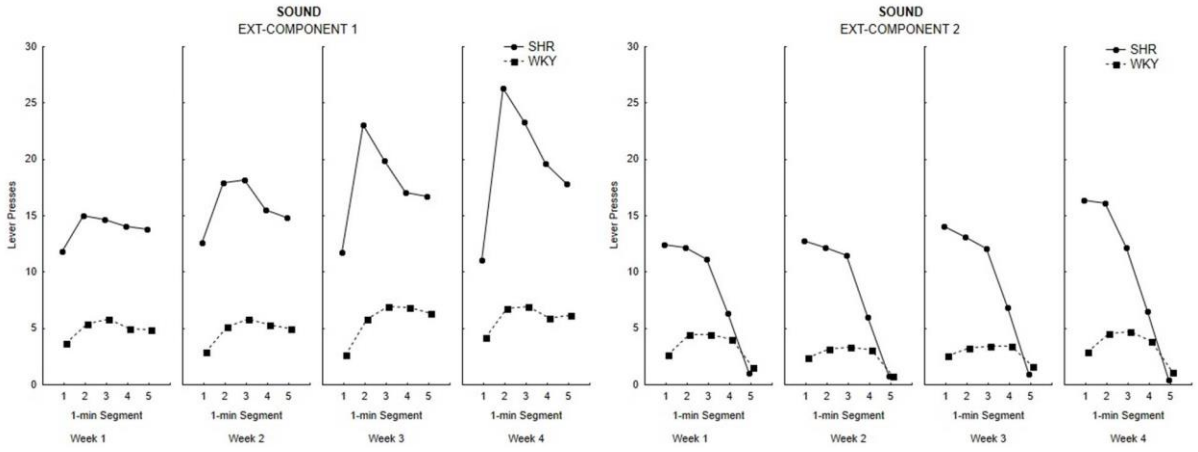

Figure 5

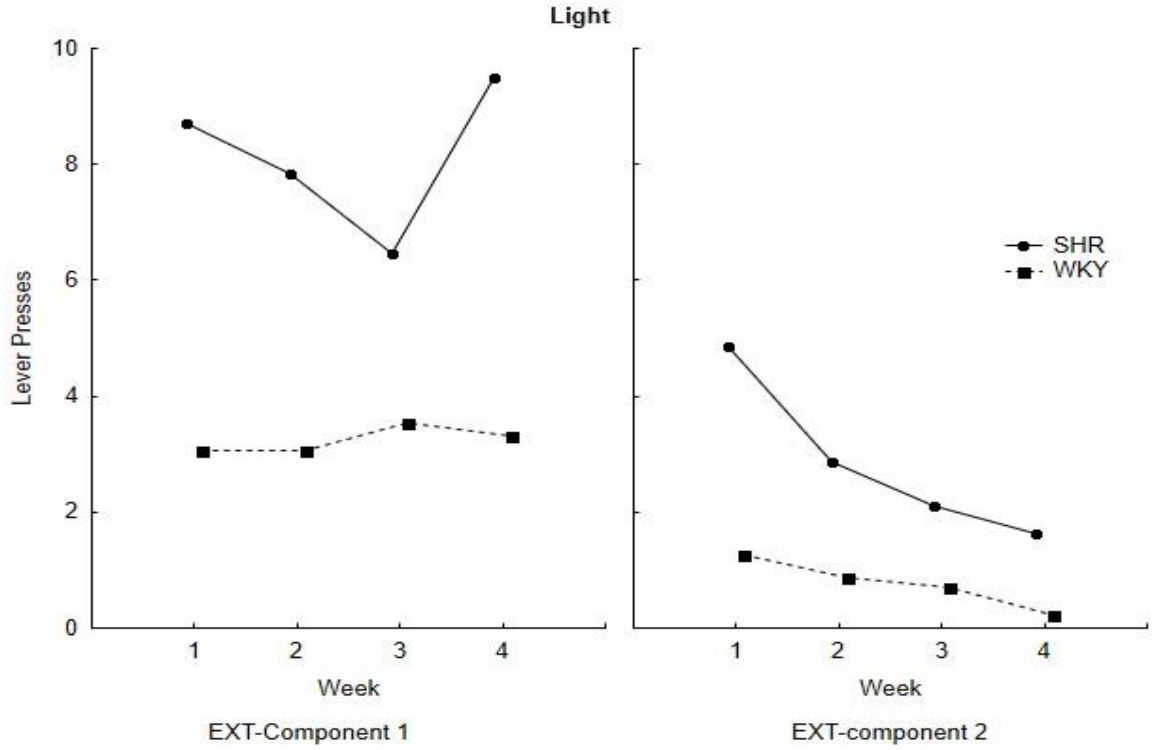

Figure 6

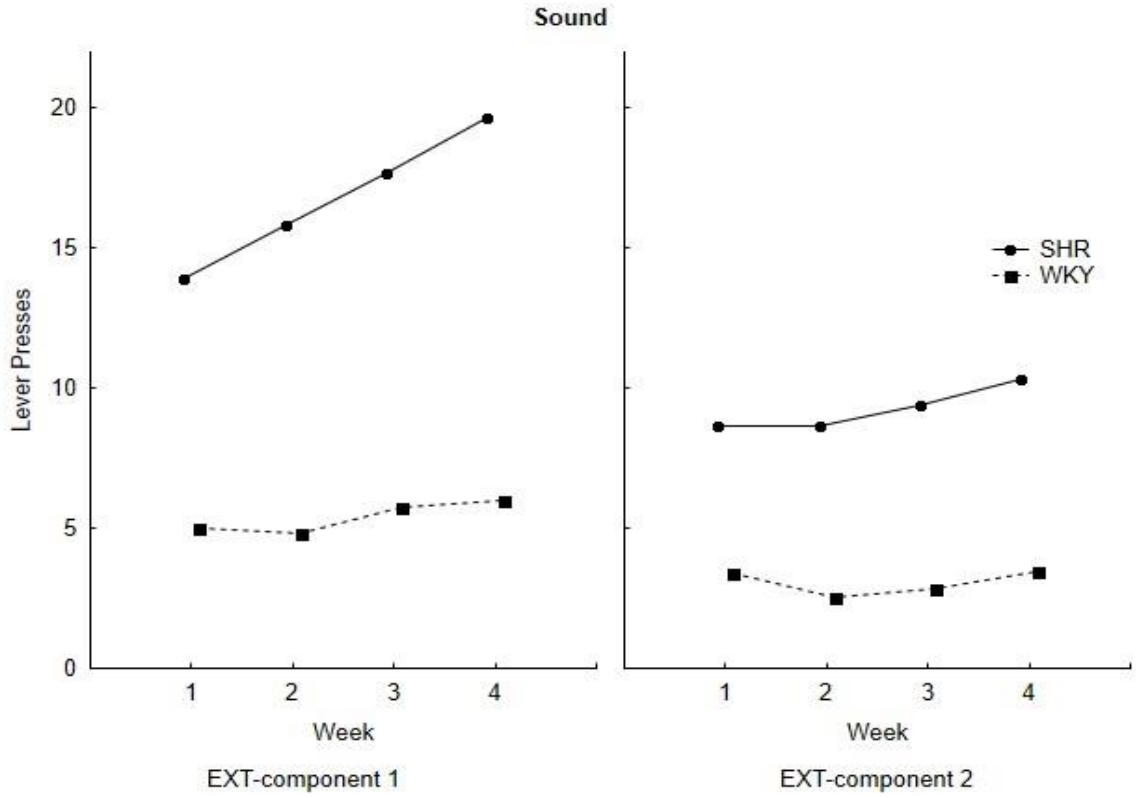

*Table 1.*Summary of the experimental procedure

*Figure 1.*Mean number of lever presses for the Light condition on the fixed-interval (FI) 2-min schedule as function of group and 10-sec segment of FI, for FI-component 1 and FI-component 2 over 4 weeks.

*Figure 2.*Mean number of lever presses for the Light condition during a the 5-min extinction (EXT) as function of group and 1-min segment of EXT, for EXT-component 1 and EXT-component 2 over 4 weeks.

Figure 3. Mean number of lever presses for the Sound condition on the fixed-interval (FI) 2-min schedule as function of group and 10-sec segment of FI, for FI-component 1 and FI-component 2 over 4 weeks.

Figure 4. Mean number of lever presses for the Sound condition during a the 5-min extinction (EXT) as function of group and 1-min segment of EXT, for EXT-component 1 and EXT-component 2 over 4 weeks.

*Figure 5.*Mean number of lever presses for the Light condition during the extinction period as functions of presence or absence of a response feedback light over the four weeks of testing for EXT-component 1 and EXT-component 2.

Figure 6. Mean number of lever presses for the Sound condition during the extinction period as functions of presence or absence of a response feedback light over the four weeks of testing for EXT-component 1 and EXT-component 2.