
# The Human-Experimental Virtual Elevated Plus-Maze as an Anxiety Model

*Das human-experimentelle virtuelle Elevated Plus-Maze als Angstmodell*

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submitted by

**Octavia Madeira**

from

**Poznań**

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Submitted on:

## Members of the Thesis Committee

Chairperson: Prof. Dr. Carmen Villmann
Primary Supervisor: Prof. Dr. Paul Pauli
Supervisor (Second): Prof. Dr. Erhard Wischmeyer
Supervisor (Third): Prof. Dr. Stefan Lautenbacher

Date of Public Defence:

Date of Receipt of Certificates:

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# Abstract

Anxiety research is one of the major psychological research domains and looks back on decades of research activity. Traditionally, novel theories and approaches are tested utilizing animal models. One way to study inherent anxiety in rodents is the elevated plus-maze (EPM). The EPM is a plus-shaped platform with two closed, i.e., walled, arms and two open unwalled arms. If given the opportunity to freely explore the apparatus, rodents instinctively avoid the open arms to protect themselves from predators. Hence, they spent less time on open and more time on closed arms, which is behaviorally associated with general anxiety. In the course of the pharmacological validation, it was found that this exploratory pattern can be reversed by anxiolytic substances, e.g., benzodiazepines, or potentiated by anxiogenics. One of the significant advantages of the EPM is that no prior training session is required in contrast to conditioning studies, thus allowing to observe natural behavior. Therefore, together with the economic and uncomplicated setup, the EPM has become a standard preclinical rodent anxiety test over the decades. In order to validate these rodent anxiety tests, there have recently been attempts to retranslate them to humans. A paramount of cross-species validation is not only the simple transferability of these animal tests but also the observation of anxiety behaviors that are evolutionarily conserved across species. Accordingly, it could be possible to conclude various factors associated with the etiology and maintenance of anxiety disorders in humans. So far, convincing translations of the EPM to humans are still lacking. For that reason, the primary aim of this dissertation is to retranslate the EPM throughout three studies and to evaluate cross-species validity critically. Secondly, the undertaken studies are set out to observe ambulatory activity equivalent to rodent EPM behavior, i.e., open arm avoidance. Thirdly, the undertaken studies aimed to assess the extent to which trait anxiety influences human exploratory activity on the platform to associate it with the assumption that rodent EPM-behavior is a reflection of general anxiety. Finally, virtual reality (VR) was the method of choice to maintain the economic advantage and adjust the EPM size to humans. Study 1 ($N$ = 30) was set up to directly transfer the rodent EPM regarding test design and experimental procedure using a Computer Automatic Virtual Environment (CAVE). The results revealed that humans unlike rodents display a general open arms approach during free exploration. However, open arm avoidance was associated with high trait anxiety and acrophobia (fear of height), which was initially assessed as a control variable due to the virtual platform height. Regression analyses and subjective anxiety ratings hinted at a more significant influence of acrophobia on open arm avoidance. In addition, it was assumed that the open arms approach might have resulted from claustrophobic tendencies experienced in the closed arms due to the high walls.

Study 2 ($N$ = 61) sought to differentiate the influence of trait anxiety and acrophobia and adapt the virtual EPM to humans. Therefore, parts of the platform held a semi-transparent grid-floor texture, and the wall height on the closed arms was reduced to standard handrail level. Moreover, participants were priorly screened to exclude clinically significant levels of acrophobia, claustrophobia, and agoraphobia. The data on general exploratory activity showed no arm preference. Regression analyses confirmed that acrophobia is related to open arm avoidance, corroborating the finding of Study 1. Surprisingly, for trait anxiety, the result of Study 1 could not be replicated. Instead, for trait anxiety, no significant effect was found indicating that predominantly fear of heights shapes human EPM behavior even on a subclinical stage. In Study 3 ($N$ = 57), the EPM was embedded into a city setting to 1) create a more natural human environment and 2) eliminate height. Furthermore, a head-mounted display was utilized for VR presentation, and arousal ratings were introduced. Participants were screened for high and low levels of trait anxiety and agoraphobia, and claustrophobia. Replicating the findings of Study 2, no difference in open and closed arm activity was observed, and no effect was found in relationship with trait anxiety. The data on anxiety ratings and claustrophobia suggest a positive correlation indicating that in this city EPM, claustrophobic tendencies might play a role in closed arm avoidance. In summary, this thesis added valuable insights into the retranslation of a well-established standard anxiety test used in rodents. However, it also majorly challenges current findings on the cross-species validity of the EPM. Various explanatory models for the results are critically discussed and associated with clinical implications concerning future research.

# Zusammenfassung

Die Angstforschung ist eines der wichtigsten psychologischen Forschungsgebiete und blickt auf eine jahrzehntelange Forschungstätigkeit zurück. Traditionell werden neue Theorien und Ansätze anhand von Tiermodellen getestet. Eine Möglichkeit, inhärente Angst bei Nagetieren zu untersuchen, ist das Elevated Plus-Maze (EPM). Das EPM ist eine plusförmige Plattform mit zwei geschlossenen, d. h. mit Wänden versehenen, Armen und zwei offenen, nicht mit Wänden umschlossenen, Armen. Wenn Nagetiere die Möglichkeit haben, die Plattform frei zu erkunden, meiden sie instinktiv die offenen Arme, um sich vor Fressfeinden zu schützen, d.h. sie verbringen weniger Zeit in den offenen und mehr Zeit in den geschlossenen Armen, was verhaltensmäßig mit Ängstlichkeit assoziiert wird. Im Rahmen der pharmakologischen Validierung wurde festgestellt, dass dieses Explorationsmuster durch anxiolytische Substanzen, z. B. Benzodiazepine, umgekehrt oder durch anxiogene Substanzen verstärkt werden kann. Einer der wesentlichen Vorteile des EPM ist, dass im Gegensatz zu Konditionierungsstudien kein vorheriges Training erforderlich ist und somit natürliches Verhalten beobachtet werden kann. Zusammen mit dem ökonomischen und unkomplizierten Versuchsaufbau hat sich das EPM daher im Laufe der Jahrzehnte zu einem Standardtest für präklinische Angstforschung bei Nagern entwickelt. Um diese Angsttests von Nagern zu validieren, wurde kürzlich versucht, diese auf den Menschen zu übertragen. Eine wichtige Voraussetzung für die artenübergreifende Validierung ist nicht nur die einfache Translation dieser Tiertests, sondern auch die Beobachtung von Angstverhalten, das evolutionär über alle Arten hinweg konserviert ist. Darauf aufbauend könnte es möglich sein, auf verschiedene Faktoren zu schließen, die mit der Entstehung und Aufrechterhaltung von Angststörungen beim Menschen in Verbindung stehen. Bislang fehlt es noch an einer überzeugenden Übertragung des EPM auf den Menschen. Aus diesem Grund besteht das primäre Ziel dieser Dissertation darin, das EPM in drei Studien neu zu übersetzen und die speziesübergreifende Validität kritisch zu bewerten. Zweitens sollen die durchgeführten Studien eine dem EPM-Verhalten von Nagetieren äquivalente Bewegungsaktivität beobachten, d.h. die Vermeidung offener Arme. Drittens zielten die durchgeführten Studien darauf ab, das Ausmaß zu bewerten, in dem Angstmerkmale das Explorationsverhalten des Menschen auf der Plattform beeinflussen, um sie mit der Annahme in Verbindung zu bringen, dass das EPM-Verhalten von Nagetieren Ängstlichkeit repräsentiert. Schließlich war die virtuelle Realität (VR) die Methode der Wahl, um die ökonomische Validität zu erhalten und das EPM in seiner Größe an den Menschen anpassen zu können. In Studie 1 ($N$ = 30) wurde das Tier-EPM hinsichtlich des Testdesigns und des Versuchsablaufs unter Verwendung einer computergesteuerten virtuellen Umgebung (CAVE) direkt auf den

Menschen übertragen. Die Ergebnisse zeigten, dass Menschen im Gegensatz zu Nagern während der freien Exploration generell eine Annäherung zu den offenen Armen zeigen. Die Vermeidung offener Arme war jedoch mit hoher Traitängstlichkeit und Akrophobie (Höhenangst) verbunden, die aufgrund der Höhe der virtuellen Plattform zunächst als Kontrollvariable erhoben wurde. Regressionsanalysen und subjektive Angstbewertungen deuteten auf einen stärkeren Einfluss der Akrophobie auf die Vermeidung der offenen Arme hin. Darüber hinaus wurde angenommen, dass die Vermeidung der offenen Arme aus klaustrophobischen Tendenzen resultieren könnte, die in den geschlossenen Armen aufgrund der hohen Wände auftreten. In Studie 2 ($N$ = 61) wurde versucht, den Einfluss von Traitängstlichkeit und Akrophobie zu differenzieren und das virtuelle EPM an den Menschen anzupassen. Daher waren Teile der Plattform mit einer halbtransparenten Gitterbodenstruktur versehen, und die Wandhöhe in den geschlossenen Armen wurde auf die Höhe eines Standardgeländers reduziert. Darüber hinaus wurden die Versuchsteilnehmer vorselektiert um klinisch signifikante Werte von Akrophobie, Klaustrophobie und Agoraphobie auszuschließen. Die Daten zu generellem Explorationsverhalten zeigten, dass keine Armpräferenz besteht. Die durchgeführte Regressionsanalyse demonstrierte, dass die Vermeidung der offenen Arme mit Akrophobie zusammenhängt, was die Ergebnisse von Studie 1 bestätigt. Überraschenderweise konnte das Ergebnis von Studie 1 in Bezug auf Traitängstlichkeit nicht repliziert werden. Stattdessen wurde für Ängstlichkeit kein signifikanter Effekt gefunden, was darauf hindeutet, dass hauptsächlich Höhenangst das menschliche EPM-Verhalten sogar in einem subklinischen Stadium prägt. In Studie 3 ($N$ = 57) wurde das EPM in eine städtische Umgebung eingebettet, um 1) eine für den Menschen natürlichere Umgebung zu schaffen und 2) den Faktor Höhe zu eliminieren. Darüber hinaus wurde für die VR-Präsentation eine Virtual-Reality-Brille verwendet, und Arousalratings eingeführt. Die Teilnehmer wurden auf hohe und niedrige Werte von Traitängstlichkeit und Agoraphobie sowie Klaustrophobie untersucht. Wie in Studie 2 konnte kein Unterschied zwischen der Explorationstendenzen der offenen und der geschlossenen Arme beobachtet werden, und es wurde kein Effekt in Bezug auf die erhobenen Angstmerkmale festgestellt. Die Daten zu Angstbewertungen und Klaustrophobie deuten auf eine positive Korrelation hin, was darauf bedeutet, dass bei diesem Stadt-EPM klaustrophobische Tendenzen eine Rolle bei der Vermeidung des geschlossenen Arms spielen könnten. Zusammenfassend lässt sich sagen, dass diese Arbeit wertvolle Einblicke in die Retranslation eines gut etablierten Standard-Angsttests für Nager liefert. Sie stellt jedoch auch die derzeitigen Erkenntnisse über die artenübergreifende Validität des EPM in Frage.

Verschiedene Erklärungsmodelle für die Ergebnisse werden kritisch diskutiert und mit klinischen Implikationen für die zukünftige Forschung verbunden.

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# Theoretical Background

Fear plays an essential role in ensuring the survival of a species as it protects the individual from life-threatening harm (Matsumoto & Ekman, 2009). Although the experience of fear or anxiety is assumed to be a healthy coping mechanism in response to threats, anxiety disorders, i.e., the chronic experience of excessive fear without a reasonable cause, rank among the most common psychiatric disorders worldwide (Bandelow & Michaelis, 2015; Baxter et al., 2013; Wittchen et al., 2011). Remarkably, one out of 14 persons meets the diagnostical criteria for an anxiety disorder at any time, which hints at the severity of this condition and the economic burden it puts on the (mental) health system (Bandelow & Michaelis, 2015; Whiteford et al., 2013). Although there are well-established psychotherapeutic interventions such as cognitive-behavioral therapy, patients often relapse (Levy et al., 2021; Scholten et al., 2013) or develop a chronic condition (Hendriks et al., 2016; Yonkers et al., 2003). Regarding pharmacological treatment, currently available medication is either accompanied by side effects that reduce patients' adherence or are not made for long-term use due to their addictive potential (Sartori & Singewald, 2019). To develop novel pharmacological agents, traditionally animal models are utilized to test anxioselective properties of the developed substances as they allow secure and ethical drug testing (Belovicova et al., 2017; Bertoglio & de Pádua Carobrez, 2016). Furthermore, animal models are used to investigate the phenomenology of anxiety disorders to deduce new therapeutic approaches for human use (Bourin, 2015; Bourin et al., 2007; Campos et al., 2013; Haller & Alicki, 2012). In doing so, the test animals, often rodents, are subdued to distinct test protocols that trigger measurable anxiety-like behaviors, which can later be compared to observed human anxiety resulting in a translational research process (Robbins, 2015). Consequently, preclinical research in animals lays the groundwork for anxiety research in humans (Cryan & Sweeney, 2011).

However, the development of novel anxioselective drugs has been on halt for over ten years as the developed test substances did not surpass the preclinical research stage (Sartori & Singewald, 2019). Therefore, questions have been raised about the transferability of these animal models recently, and critics even imply that these models suffer from a lack of translational validity, causing this scientific paucity (Stanford, 2017; Steimer, 2011). As a result, recent years have witnessed a growing academic interest in the scientific review of the cross-species validity of rodent anxiety models. In the meantime, fear conditioning looks back on a translational success story as these test protocols have been successfully validated for both humans and rodents (Haaker et al., 2019). However, data on the cross-species validity for non-

conditioning rodent anxiety tests are fragmentary and do not allow substantial conclusions yet (Grillon & Ernst, 2016).

In the sight of this blind spot within human anxiety research, this thesis aims to explore the translation of the elevated plus-maze (EPM), which is one of the most common unconditioned rodent tests for anxiety, using virtual reality (VR).

## 1.1 Anxiety Research in Animals

### 1.1.1 Theories and Concept

In preclinical anxiety research, rodents are the most frequently used test animal as their ethology is thoroughly documented already, and they are easy to handle (Baumans, 2016). In preclinical psychiatric research, in particular, rats are preferably utilized since they are easier to train, facilitating the implementation of, for example, fear conditioning protocols that will later be discussed in detail (Bertoglio & de Pádua Carobrez, 2016). The following chapter will overview anxiety research in rodents in general and point out various essential methods and tools.

#### *1.1.1.1 Anxiety in Rodents*

We know that rodent anxiety is primarily based on observing changes in behavioral parameters resulting from experimental manipulation (Bertoglio & de Pádua Carobrez, 2016; Ohl, 2003). Coming from basic rodent ethology, the species-specific defensive reaction theory (SSDR) proclaims that rodents have a set of distinct defensive behavioral patterns if faced with a potential (life) threat, for instance, the appearance of a predator (Bolles, 1970; Whishaw & Kolb, 2004). In their work, Fanselow and Lester (1988) formulated the idea that these behaviors can be assigned to different phases (Pre-Encounter, Post-Encounter, Circa-Strike) depending on a predator's spatial and temporal proximity and also represent different states of anxiety (*Predatory Imminence Continuum Theory*). In the first phase (Pre-Encounter), the animal assumes the presence of a predator based on previous experiences or instincts. Therefore, the displayed behavior is characterized by risk-minimizing strategies to avoid encountering a said predator (Mobbs et al., 2019). As a result, the rodent, on the one hand, engages in exploratory activities such as stretched approaches or an increase in vigilance while on the other hand pre-plans an assumed encounter by altering food intake routines (Barnett, 2017; Mobbs et al., 2019; Perusini & Fanselow, 2015). Thus, the Pre-Encounter phase conceptually refers to anxiety (Fanselow & Lester, 1988; Mobbs et al., 2019). If a predator or an immediate threat is detected (Post-Encounter phase), the rodent takes on behaviors that decrease the risk of being detected or attacked, e.g., thigmotaxis (moving along walls) or freezing (Mobbs et al., 2019).

Consequently, this stage in the model is associated with fear. Finally, if a predator is about to attack (Circa-Strike phase), the rodent enters a panic-like fight-or-flight state in an attempt to protect itself from life-threatening harm or even death by engaging in self-defense behavior or escape (Fanselow, 1994; Helmstetter & Fanselow, 1993; Mobbs et al., 2019; Perusini & Fanselow, 2015).

Given the theoretical and ethologic background described above, preclinical animal research is based on creating experimental environments and methods that trigger these defensive behaviors to investigate variables that mitigate, eliminate, or intensify them to conclude anxiety- or fear-related processes (Blanchard et al., 2003; Blanchard & Blanchard, 1989; Blanchard et al., 1989; Fanselow & Ponnusamy, 2008). For example, in the Vogel conflict test, rats are first deprived of water and then provided a beverage associated with an aversive electric stimulus acting as a fear-inducing punishment (Vogel et al., 1971). Consequently, this elicits an approach-avoidance conflict, as a basic physiological need (thirst) needs to be satisfied (approach) at the cost of exposing oneself to a potentially life-threatening situation associated with anxiety (avoidance) (Basso et al., 2011; Vogel et al., 1971). As a result, the test animal is exposed to a situation in which it needs to quantify the cost-benefit of these opposing behavioral alternatives. Accordingly, the factors influencing this decision hint at the specific role of anxiety-modulating variables. For example, regarding the Vogel conflict test, it was found that the application of benzodiazepines, i.e., anxiolytic agents, leads to increased drinking, which is interpreted as a decrease in anxiety (Basso et al., 2011; Mathiasen & Mirza, 2005). Another sample for the systematic test of defensive behaviors in rodents is the Mouse Defense Test Battery, in which the animal is suddenly exposed to predator (cat) odor in its natural habitat (Blanchard et al., 2003). Consequently, this prompts defensive behavioral patterns, e.g., freezing or flight, interpreted as fear- or panic-like behaviors (Blanchard et al., 2003; Griebel & Sanger, 1999; Yang et al., 2004). Like the Vogel conflict test, the application of anxioselective drugs modifies these defensive behavioral patterns and thus pharmacologically validates the test (Blanchard et al., 1990; Blanchard et al., 2003). In summary, it can be said that traditionally distinct behavioral patterns, which are part of the ethologic repertoire of rodents, and their alteration in response to experimental manipulation are interpreted as anxiety or fear. In this, typical anxiety indices derive from the observation of *exploration* and *approach*/*avoidance behavior* which are usually transcribed as spatiotemporal ("time spent in x area") or quantitative ("number of actions") variables (Belzung & Griebel, 2001; Dielenberg & McGregor, 2001; Yang et al., 2004). In line with the Predatory

Imminence Continuum model, these data also cover subtle behavioral patterns summarized under *risk-assessment behavior* (Blanchard et al., 2011).

In addition, biomarkers are routinely measured to research physical manifestations of anxiety and reach conclusions about neural or endocrinologic pathways. For instance, the startle response is a protective reflex elicited by sudden and strong sensory stimuli and leads to a brief and involuntary stiffening of body parts (Geyer & Swerdlow, 1998; Landis & Hunt, 1939). In almost all mammals, it can be observed that it is potentiated by fear (*fear-potentiated startle response*) and controlled and modulated by several neural regions and substrates (Davis, 2006; Davis et al., 1993; Hamm, 2015; Yeomans & Frankland, 1995). Specifically, it was, for example, found that glutamate receptors of the amygdala are involved in startle reflex modulation, which is an excellent example of how precise nowadays methods can be (Tran et al., 2013; Walker & Davis, 2002). Furthermore, plasma corticosterone levels, an endocrinologic marker of a stress response, are also utilized to evaluate short- or long-term effects of stress-inducing procedures on anxiety (Kinn Rød et al., 2012; Rodgers et al., 1999). Lesion studies help in giving much more precise insights by specifically targeting brain areas that were identified in playing a significant role in anxiety, e.g., the amygdala, the hippocampus, and the prefrontal cortex (Barkus et al., 2010; Cominski et al., 2014; Shiba et al., 2016; Weeden et al., 2015). Also, targeting the function of specific genes via gene knockout aided tremendously in identifying underlying molecular mechanisms and genetic predispositions (Wood & Toth, 2001).

A much-debated question is the examination of *cognition* and *emotion* in rodents, as these require higher cognitive abilities and, most importantly, a suitable measurement method. Whereas in humans, verbal responses or, although controversial (Barrett et al., 2019; Gendron et al., 2014), facial expressions can be valid indicators of emotionality on numerous qualitative levels and allow more significant insights into invisible processes, this possibility is not available in rodents (Berridge & Scherer, 2003; Ekman, 1992). Therefore, preclinical neuroscience examines behavioral and psychophysiological responses to presented stimuli only (Berridge & Scherer, 2003). Although studies found that (infant) rats are capable of ultrasonic vocalization to communicate their own and alter emotional states in other rats (Brudzynski, 2013; Wöhr & Schwarting, 2013), even in this case, the studies have relied on the traditional behavioral outcome measures and thus perpetuate the narrative.

Despite severe limitations, classic animal tests have provided deep insights into anxiety processes on a behavioral, genetic, and pharmacological level, which justify their use in preclinical trials until today.

### 1.1.2 Research Paradigms in Rodents

#### *1.1.2.1 Fear Conditioning*

Dating back to the 1920s (Pavlov & Anrep, 1927), fear conditioning has a long history in animal research and represents one of the most used paradigms in fear research until today. For fear conditioning, the test protocol consists of at least two stages. Firstly, during the acquisition phase, a neutral stimulus, e.g., a tone (CS, conditioned stimulus), or an environment (CTX, conditioned context) is repeatedly paired with an unpleasant, often painful stimulus, e.g., an electric foot shock (US, unconditioned stimulus) (Curzon et al., 2009). This then elicits a species-specific fear reaction (UR, unconditioned response), for instance, avoidance or freezing (Haaker et al., 2019; Lonsdorf et al., 2017). Secondly, in the test phase, the former neutral CS or the CTX is presented without the US triggering a fear reaction, now a conditioned reaction (CR), without the presence of the aversive stimulus (Curzon et al., 2009; Kamprath & Wotjak, 2004; Milad et al., 2011; Wehner & Radcliffe, 2004) as there now exists a robust learned association between the CS or CTX and the US.

Nowadays, fear conditioning is utilized to investigate a variety of fear-associated issues. In doing so, the research community traditionally distinguishes between cue- and context-conditioning (Wotjak, 2019). Both methods follow the same test protocol described earlier but refer to different types of fear. Here, a cue usually refers to a substantial distinctive element (tone, odor), whereas a *context* is defined as "a conjunctive holistic representation of the test situation […]" (Wotjak, 2019, p. 34), for instance, reflected in cage shape (rectangular vs. round). Conceptually, cue-based conditioning examines phobic-related fear processes and behaviors, as the aversive event, i.e., electric shock, is associated with a unique and distinguishable entity within the test environment (Curzon et al., 2009; Lonsdorf et al., 2017; Milad et al., 2011). Furthermore, given the Predatory Imminence Model (Fanselow & Lester, 1988; Perusini & Fanselow, 2015), cue conditioning examines processes affiliated to the Post-Encounter phase and serves as a precursor of specific phobias in humans (McNally, 1987). In contrast, in context conditioning, the relationship of the aversive stimulus and distinct environmental features remains ambiguous, leading to a hypervigilant state (Curzon et al., 2009; Wehner & Radcliffe, 2004). From a phenomenological point of view, this state matches the Pre-Encounter stage and refers to anxiety (Curzon et al., 2009; Haaker et al., 2019; Lonsdorf et al., 2017; Walker et al., 2009).

To date, several studies investigate how fear is acquired and "unlearned". For a long time, it was assumed that in *extinction learning*[1] the CS-US association is basically deleted (Fanselow & Ponnusamy, 2008). However, several lines of evidence together with findings on studies using *reinstatement*[2] suggest that this trace is not unlearned or altered but instead remains, and a second parallel CS-US link is created, leading to a *return of fear* (Bouton, 2002; Craske & Mystkowski, 2006; Cryan & Holmes, 2005; Curzon et al., 2009; Lonsdorf et al., 2017; Milad et al., 2011; Milad et al., 2006). In contrast, operant conditioning protocols introduce behavioral tendencies that are either reinforced or punished to increase or decrease their probability of occurrence (Skinner, 1938). In doing so, the *reinforcement rate* is modified via experimental manipulation (Milad et al., 2011).

By using these approaches, researchers have gained in-depth insights into fear conditioning in general and topics like fear learning, fear memory, molecular and neurological functions, and brain circuits associated with it (Haaker et al., 2019; Tovote et al., 2015). In this, it has to be noted that these findings set the foundation for anxiety research in humans and provided fundamental insights into understanding anxiety disorders and their treatment from a translational perspective (Delgado et al., 2006).

#### *1.1.2.2 Naturalistic Approaches*

In rodent anxiety research, naturalistic approaches refer to the observation of anxiety without a previous training or conditioning protocol (Belovicova et al., 2017; Belzung & Griebel, 2001; Bertoglio & de Pádua Carobrez, 2016). Therefore, unlike fear conditioning, these tests are considered detached from a strict experimental protocol and are among the standard equipment in the rodent anxiety laboratory nowadays (Bertoglio & de Pádua Carobrez, 2016).

#### *1.1.2.3 Open Field Test*

The Open Field Test (OFT) is a rectangular or round-shaped space with walls where the rodent is confined. Hall (1934) developed the OFT to examine rodent behavior in a literal open field and assumed, based on ethological knowledge, that defecating is a behavioral index for timidity. Due to its instincts, the rodent naturally avoids open spaces to prevent encounters with aerial predators and thus displays defensive behaviors such as thigmotaxis and the avoidance

[1] In extinction learning, the test animal is exposed to the CS (e.g., acoustic signal) without the US (e.g., electric foot shock) (Lonsdorf, et al., 2017).
[2] In the utilization of a reinstatement protocol, only the US without the CS is presented (Haaker, et al., 2019ibid.)

of central areas of the field (Gould et al., 2009; Prut & Belzung, 2003; Seibenhener & Wooten, 2015; Walsh & Cummins, 1976).

In this respect, the OFT is now considered a standard anxiety test and traditionally plays a significant role in the detection of anxiolytic drug properties, which are behaviorally reflected in a decrease in thigmotaxis and freezing along with an increase in central crossings (Choleris et al., 2001; Rex et al., 1998).

However, newer research trends aim to identify endogenous, preferably genetic, vulnerability factors of anxiety with the help of the OFT. For instance, it has been shown that 5-HTT knockout rats and mice lacking serotonin transporter activity display more thigmotaxis and less center exploration than controls, which makes this genotype a promising animal model for (pathologic) anxiety in humans (Holmes et al., 2003; Kalueff et al., 2007; Kalueff et al., 2010; Krakenberg et al., 2019). Also, several studies have postulated a connection of 5-HTT genotypes to anxiety disorders in humans based on this preclinical research (Gottschalk & Domschke, 2017; Kobiella et al., 2011; Schiele et al., 2016).

Despite the numerous scientific breakthroughs with the help of the OFT described earlier, one cannot neglect various limitations. In fact, the OFT continuously lacks standardization across several studies as there still exists no test protocol. As illustrated in the reviews of Walsh and Cummins (1976) and Prut and Belzung (2003), OFT details on size, shape (round vs. rectangular), wall height, illumination level, and exposure duration (minutes vs. hours) often vary from lab to lab. The authors condemn the lack of specification in publications within the research community, which aggravates the replication of the conducted studies and impairs the comparability of results across studies (Prut & Belzung, 2003; Walsh & Cummins, 1976). However, while the absence of standards states a major methodological drawback, the OFT still has its rationale. In this perspective, open field exploration is not the only criterion in evaluating the influence of either genetic modifications or compound effects as the OFT is usually part of a test battery for a holistic experimental perspective (i.e., Holmes et al., 2003).

#### *1.1.2.4 Dark-Light-Box Test*

The conceptual basis of the Dark-Light-Test relies on rodents' natural tendency to explore novel environments versus their avoidance of brightly illuminated spaces and thus elicits an approach-avoidance-conflict (Crawley & Goodwin, 1980b). The Dark-Light-Box consists of two compartments, one dark or sparsely illuminated section, whereas the other section is brightly illuminated, creating an anxiogenic environment (Crawley & Goodwin, 1980b; Lister, 1990). In this respect, an increase in compartment transitions indicates activity and low anxiety, whereas time spent in the dark area indicates rodent anxiety (Bourin &

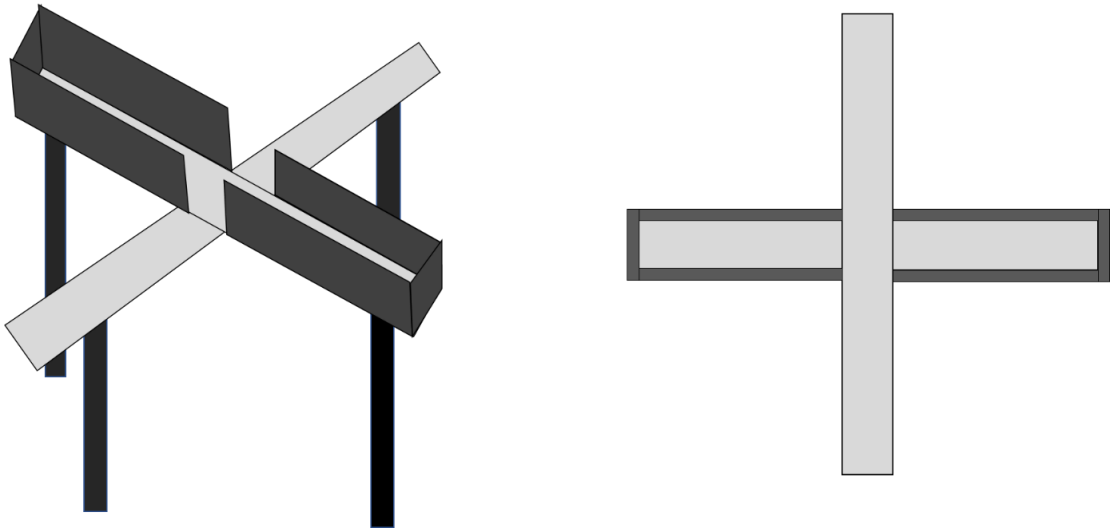
Hascoët, 2003; Hascoët & Bourin, 2009; Lister, 1990). Initially, the test was developed solely for male mice to validate the anxiolytic effect of benzodiazepines, and it was observed that the application of them led to an increase of transitions between the two compartments and time spent in the brightly illuminated area (Arrant et al., 2013; Crawley & Goodwin, 1980a; Harro, 1993, 2018). Thus, regarding the detection of anxiolytic pharmacological agents, the Dark-Light-test queues up with other rodent exploratory tests and is a standard procedure in the rodent laboratory. However, research protocols frequently differ from lab to lab. For example, some laboratories keep a tally of the light to dark transitions, whereas others refer to the dark to light transitions.

Nevertheless, the Dark-Light-Box is a standard test in rodents' research until today and is utilized along with other behavioral tests to determine the extent of anxiolytic or anxiogenic effects of many variables, preferably pharmacological agents (Bourin & Hascoët, 2003).

#### *1.1.2.5 Elevated Plus-Maze*

In order to examine the exploratory behavior of rats, Montgomery (1955) designed a Y-Maze, an elevated platform with one open and one enclosed arm, and found that test rodents avoid the open arm more. Based on this finding, Pellow et al. (1985) developed the elevated plus-maze (EPM) to validate the effect of pharmacological agents by observing its effects on exploratory behavior on the maze. The EPM is a plus-shaped maze usually elevated to 50 cm in height with two open, i.e., unwalled arms and two closed arms (see **Figure 1).** In a series of

**Figure 1.** The rodent elevated plus-maze (EPM)



Schematic drawing (left) and top view (right) of the EPM. Mice or rats are placed in the center area, facing one of the arms, and have five minutes to explore the platform freely. Typically, rodents show a general open arm avoidance (Pellow et al., 1985).

experiments, Pellow et al. (1985) placed the test animals in the center area of the EPM and gave them five minutes to explore the platform freely. In doing so, they reported that rats display a general open arm avoidance, and that this tendency can be manipulated by applying anxiolytics, e.g., benzodiazepines, barbiturates, and anxiogenics, e.g., yohimbine, amphetamine (Pellow et al., 1985). The authors demonstrated that anxiolytics increase open arm activity, whereas anxiogenics diminish it (Pellow et al., 1985). As a control condition, they also tested anti-depressants (Mianserin, Imipramine) and antipsychotic medication (Haldol) and found no or contradictory effects on maze ambulation patterns (Pellow et al., 1985). Therefore, they deducted, that the EPM is a test of rodent anxiety. The innovative and seminal work of Pellow et al. (1985) pioneered a new approach by providing the opportunity to examine anxiolytic *and* anxiogenic compound characteristics simultaneously.

Follow-up studies not only iterated the importance of the EPM as an anxiety test but also identified additional variables like handling history of test animals (Andrews & File, 1993; Gouveia & Hurst, 2013; Hurst & West, 2010; Ueno et al., 2020), animal age, gender and circadian rhythm (Albani et al., 2015; Andrade et al., 2003; Bertoglio & Carobrez, 2002; Imhof et al., 1993) and predator odor (Adamec & Shallow, 1993; de Paula et al., 2005) among many others to influence exploration behavior on the maze (Korte & De Boer, 2003). Furthermore, the EPM was also validated for other species, e.g., mice and even fish (e.g., Carobrez & Bertoglio, 2005; File, 1993; Hogg, 1996; Hope et al., 2019; Komada et al., 2008; Lister, 1987; Rodgers & Dalvi, 1997; Walf & Frye, 2007). Interestingly, there is evidence that platform height does not play a significant role, potentially disqualifying height as a modulating or even anxiogenic variable (Martínez et al., 2002; Treit et al., 1993). Furthermore, it was also detected that extended and repeated EPM exposure does not lead to habituation, that a single maze experience acts as anxiogenic itself, increases open arm avoidance, and even abolishes the anxiolytic effect of benzodiazepines in subsequent test trials (Bertoglio & Carobrez, 2000; Cruz-Morales et al., 2002; Lister, 1987; Rodgers & Shepherd, 1993; Schrader et al., 2018; Treit et al., 1993). This so-called *one-trial tolerance* (OTT) is an intensely discussed topic and different theories exist in the literature regarding its cause (Carobrez & Bertoglio, 2005; File, 1990). For instance, it has been hypothesized that OTT originates in a learned response that is a result of an uncontrolled conditioning process leading to a phobic state in the second trial (File & Zangrossi, 1993). Today, the EPM has become a standard test for animal anxiety in various areas resulting in almost 10,000 publications so far (Web of Science, 2020). Therefore, the EPM is considered a test of general anxiety in rodents and part of the standard practice in preclinical rodent anxiety research.

Nevertheless, there remain controversial topics within the research community, such as the maze performance outcome variables. Nowadays, rodent exploration behavior is recorded and analyzed via tracking software to avoid manual observer errors (Ari et al., 2019; Kraeuter et al., 2019; Sidor et al., 2010). Here, the results mainly report on spatiotemporal measures such as (% of) open/closed arm time or the number of arm entries. However, most of the EPM-studies have insufficiently addressed center area activity and its implication for anxiety. Whereas some authors merge center area and closed arms, defining it as a "safe space" on the maze, others refer to its ambiguity and suggest excluding it from final analyses (Fernandes & File, 1996; Hogg, 1996). As Fernandes and File (1996) point out in their analysis, time spent in the center area generally refers to motor activity rather than anxiety, a factor that the sedative effect of benzodiazepines can impair. Nonetheless, "center time" is often reported without further explanation. Meanwhile, some authors acknowledge the controversy and aim to invent the "zero-maze", a circular platform with open and closed zones, avoiding a proper center area (Shepherd et al., 1994). Thus far, several studies have demonstrated and highlighted that the zero-maze elicits comparable results to the traditional EPM (Braun et al., 2011; Tucker & McCabe, 2017).

Another point of criticism pertains to the outcome measures mentioned before. Most of the studies reviewed so far suffer from the fact that EPM behavior is mainly analyzed through time spent on the maze areas, preferably open arms, or number of arm entries only. While this on the one hand is an economical way of data collection, which is done effortlessly through specific programs, it neglects important, more nuanced behavioral patterns. In their review on the EPM, Rodgers and Dalvi (1997) advocate for the comprehensive ethologic data collection, as the data of several studies suggest an enhanced sensitivity for anxiolytic and – genic compounds. In the authors' view, this improves the validity and might help spot anxioselective effects in (novel) non-GABAergic substances (Rodgers & Dalvi, 1997; Rodgers & Johnson, 1995; Rodgers, Perrault, et al., 1997). Accordingly, there have been attempts in expanding the list of measurable behavioral parameters, but results remain contradictory and inconsistent (Casarrubea et al., 2016; Casarrubea et al., 2013; Sorregotti et al., 2013).

### 1.1.3 Summary and Critique

The techniques and methods mentioned above set the foundation of anxiety research in both animals and humans translationally. We know about the functional, behavioral, and pharmacological basics of anxiety because of them. Nevertheless, fear conditioning and non-conditioned paradigms hold certain limits that need to be discussed.

A central point of discussion concerns inconsistencies regarding protocol standardization. As briefly outlined earlier, many factors influence behavioral performance in conditioning and naturalistic experiments. However, the research has not sufficiently accounted for all aspects of these variables, which leads to significant variability in nomenclature, equipment design, or materials. For instance, there exists a significant variability regarding the shape of the OFT, i.e., circular vs. rectangular, and test duration ranging from five minutes to hours noticeable throughout the literature (Stanford, 2007). These methodological fluctuations were disapproved of very early on but were often neglected, and it was not until 2014 when Grabovskaya and Salyha (2014) showed that OFT shape does not affect OFT behavioral performance. However, the research community has failed to address these inconsistencies continuously for other variables. The reproach about the lack of standardization also applies to the Dark-Light-Test and the EPM. Therefore, in their review, Bourin and Hascoët (2003) point out the numerous constructional and methodological modifications and address the inconsistencies in the findings. To date, several studies reported that the level of illumination (Garcia et al., 2005; Kulesskaya & Voikar, 2014), animal sex, and age (Albani et al., 2015; Armbruster et al., 2018; Arrant et al., 2013; Cover et al., 2014) as well as handling history (Andrews & File, 1993; Gouveia & Hurst, 2013; Ueno et al., 2020) can alter test performance apart from the experimental manipulation. In this respect, it is surprising that material details and lab surroundings are often scarcely reported in the literature, which in return aggravates replication studies and possibly leads to the discourse of inconsistent findings.

Furthermore, the prior test experience is a critical aspect as well, especially when considering that most of these rodent anxiety tests are built on the concept of novelty (Bouwknecht et al., 2004; Cowan & Richardson, 2018; Gouveia & Hurst, 2013; Schöner et al., 2017). Although these anxiety test batteries are often utilized to cover the entire spectrum of anxiety behaviors in response to experimental manipulations, only very few studies have systematically examined transitory test effects (Ramos, 2008; Sudakov et al., 2013). So far, researchers conducted a factor analysis to associate behavioral parameters with either general activity or anxiety and found that the “classic” anxiety indices in the “classic” tests, e.g., open-arm-entries on the EPM vs. center crossings in the OFT vs. light/dark transitions, do not consistently load on the same factor, i.e., anxiety, but can also represent locomotion (Díaz-Morán et al., 2014; Henderson et al., 2004). In other words: test performances rarely correlate with each other, and the effects of test sequences are not entirely explained yet (Hu et al., 2017; Snyder et al., 2021; Sudakov et al., 2013; Thiel et al., 1999). For instance, McIlwain et al. (2001) examined the effects of test experience in mice using standard behavioral tests and found

significant differences in test performance between test experienced vs. test-naïve mice. Likewise, Võikar et al. (2004) corroborated these findings in their studies and hint at the influence of strain type. Under those circumstances, one can assume that the everyday use of test batteries is a powerful tool in preclinical science but needs to be applied with caution.

Concerning rodent strains, selective breeding of "anxious" strains aimed at identifying genetic as well as molecular precursors for anxiety and now serve as animal models of anxiety (disorders) in humans (Neumann et al., 2010; Neumann et al., 2011). Despite the numerous scientific insights gained by them, this concept has been challenged by studies reporting that the different genotypes also significantly vary in anxiety-related behaviors (Bolivar et al., 2000; Camp et al., 2012; Hall et al., 2009). In fact, numerous studies identified varying baseline exploration patterns in rat strains that, consequently, confound comparison of movement data across multiple studies executed with different strain types in unconditioned tests (Clément et al., 2002; Crabbe et al., 1999; Ramos et al., 2003; Ramos et al., 2008). Likewise, the rodent strains differ in shown fear behavior in fear conditioning protocols, i.e., they vary regarding fear-related response (Gomes et al., 2013; López-Aumatell et al., 2009; Ramos et al., 2003; Steiner et al., 2011). For example, Graham et al. (2009) reported that Sprague Dawley rats displayed more freezing responses and ultrasonic vocalization compared to Long-Evans rats in a Pavlovian fear conditioning protocol. Moreover, genetic modification can also lead to an altered reactivity to pharmacological agents (Belzung & Barreau, 2000; Tejani-Butt et al., 2003). For instance, C57BL/6J mice, a widely used mouse strain, are more sensitive to anxiogenics than anxiolytics, leading to a significant reduction or even the absence of anxiolytic effects of low-dose anxiolytics (Heredia et al., 2014; Kalueff & Nguyen, 2014).

Meanwhile, the call for detailed observation of behavioral measures has a long history already. Several researchers already highlighted the importance of measuring behavioral risk assessment patterns instead of exclusively observing spatiotemporal variables as they are more sensitive to anxiolysis (Carobrez & Bertoglio, 2005; Cruz et al., 1994; Rodgers & Johnson, 1995). For instance, testing a cohort of undrugged DBA/2 mice revealed that among the traditional variables also the percentage of stretched attended postures (SAP) is an index of anxiety on the EPM (Rodgers, Cao, et al., 1997; Rodgers, 1997). However, the detailed observation requires extensive training of the observers, and even then, the number of distinct behaviors to simultaneously observe is limited. Nevertheless, the discrete evaluation of specific etiologic features allows more profound insight into non-conditioned experimental settings even though it might complicate experimental procedure and the data analyses.

## 1.2 Anxiety Research in Humans

### 1.2.1 Anxiety in Humans

As fear plays a pivotal role in protecting the individual against potential (anxiety) or acute (fear) life-threatening dangers, it is of vital importance within the defensive emotional range and is classified as a basic emotion (Ekman, 1992; Fanselow, 1989; Matsumoto & Ekman, 2009). Early theories assumed that emotions are merely the result of a physiological process within the brain or peripheral nerve system (Sander, 2013). In contrast, Lang (1978) assumed that human emotions manifest on three levels interacting with each other: 1) facial expression or speech, 2) change in physiological states attached to autonomic and somatic systems, and 3) behavior. Meanwhile, newer theories suggest the existence of both top-down and bottom-up processes on various levels for anxiety in humans (see Sander, 2013 for a detailed discussion). Nowadays, the research community agrees that cognitions also play an essential role in the appraisal and control of human anxiety (LeDoux, 2014; Robinson et al., 2013; Spielberger, 1972). In particular, it has been proposed that the experience of the emotion *fear* is an interplay of all the elements mentioned above in addition to individual experiences (traumatic or not), learning mechanisms, neurophysiological (brain) circuits, available cognitive resources, and attention processes (Barlow, 2000).

Consequently, the measurement of anxiety and fear in humans is multimodal. What stands out is that human anxiety research profits from verbal communication, which only makes it possible to provide insights into cognitive processes. Thus, in contrast to animal anxiety research, research on human anxiety and fear benefits from subjective *and* behavioral measurements (Grillon et al., 2006). What also exceeds animal research is the analysis of emotional facial expressions, verbal feedback considering valence and arousal in reaction to emotional stimuli like, for instance, the IAPS (Lang et al., 1997). Therefore, throughout the decades of research, multiple aspects of anxiety have been observed, examined, and conjoined to complete the picture.

#### *1.2.1.1 Fear vs. anxiety and state vs. trait*

The Predatory Imminence Model is also applicable to humans and differentiates between anxiety and fear (Blanchard et al., 2001). Equivalent to rodents, humans display distinct defensive behaviors dependent on threat proximity. They either engage in risk assessment if hearing a strange noise at night (Pre-Encounter stage, anxiety), attempt to hide or prepare to attack if receiving a strange or threatening phone call (Post-Encounter stage, fear) or attack or run if an unknown person suddenly strikes (Circa-Strike, panic) (Blanchard, 2017;

Blanchard et al., 2001). Nevertheless, in human research, the term anxiety refers to a hypervigilant state in a potentially threatening situation and a personality disposition (trait anxiety). In the 1950s, Catell and Scheier (1958) conducted a factor analysis and identified two anxiety factors. They found that one factor referred to a more unstable and transient condition in reaction to acute events (*fear*) and the other factor indicates a stable personality feature (*anxiety*) associated with the proneness to react with fear (Catell & Scheier, 1958). Later, Spielberger et al. (1970) took up this theory of an existing anxiety dichotomy and developed a questionnaire based on it, which nowadays is an established tool in assessing individuals' levels of trait (anxiety) and state anxiety. Subsequent studies aimed at establishing a more detailed distinguishment of these two concepts and several other theories. For instance, Öhman (2008, as cited in Sylvers et al., 2011) assumes that fear is an active coping mechanism in response to a concrete threat, whereas anxiety stems from the inability to cope with an ambiguous threat. This is comparable to the cognitive appraisal theory of Lazarus and Folkman (1984), who hypothesized that coping with stressors leads to a negative form of stress with negative psychological long-term effects. In his overview, Öhman (2008) categorizes several experimental approaches to target the two anxiety components and critically discusses unconscious processes of them. Numerous studies support the theory of top-down modulation of (trait) anxiety. For instance, it was found that an individual's level of trait anxiety is positively associated with an attention bias towards threatening visual stimuli, e.g., angry faces (Dodd et al., 2017; Koster et al., 2005). Other research groups make a similar point by finding out that high trait anxious subjects lack attentional control in general, leading to a deficiency in inhibitory control towards perceived threats (Archer, 1973; Pacheco-Unguetti et al., 2010). Therefore, if they find themselves in an ambiguous situation, for instance, a dark alley, almost everything, maybe even their own shadow, becomes a threat. It is therefore not surprising that high levels of trait anxiety are a known risk factor for the development and preservation of anxiety disorders (Hofmann et al., 2009; Kindt & Soeter, 2014; Mogg & Bradley, 2016; Ormel et al., 2004; Soeter & Kindt, 2013).

On the other hand, it was found that increased state anxiety leads to a negative interpretation bias and compromises emotion recognition towards negative or ambivalent stimuli suggesting a bottom-up process (Attwood et al., 2017; Mathews & Mackintosh, 2000; Quigley et al., 2012). Studies using a fear conditioning protocol found that elevated state anxiety levels are linked to return of fear, enhanced generalization, and diminished fear discrimination (Dibbets & Evers, 2017; Kuhn et al., 2016).

Introducing the concept of anxiety sensitivity, Reiss et al. (1986, p. 1) proposed that there are individuals who uphold " beliefs that anxiety experiences have negative implications". In order to avoid any possibility of confusion with trait anxiety, Reiss et al. (1986) were determined to differentiate between the two notions. Thus, they outlined anxiety sensitivity as a future-oriented concept as the individual does not focus on a present potential threat per se but fears negative consequences if fear is experienced (McWilliams & Cox, 2001; Taylor et al., 1991). For instance, individuals with high levels of anxiety sensitivity might fear that if they experience fear in any context leading to increased sweating, they might look stupid and thus become unlikable. As a result, this individual will either avoid social situations or experience a high amount of fear or even panic if exposed to them (Schmidt et al., 1997). Because of this pathway, anxiety sensitivity is seen as a salient risk factor in the pathogenesis of panic attacks and panic disorder and other anxiety disorders, i.e., agoraphobia (McNally, 2002; Plehn & Peterson, 2002; Rodriguez et al., 2004; Schmidt et al., 1997). In contrast, trait anxiety is clinically associated with Generalized Anxiety Disorder (GAD) and affective disorders like major depression (Bados et al., 2010; Brenneisen Mayer et al., 2016; Endler & Kocovski, 2001; Eysenck, 1992). Nevertheless, the categorical nature of state and trait anxiety has long been a controversial discussion topic. For instance, Endler and Kocovski (2001) suggest a multidimensional construct and even advocate for an interaction model of anxiety, stress, and coping mechanisms.

#### *1.2.1.2 Excursus: Anxiety Disorders*

The DSM-5 defines anxiety disorder as "disorders that share features of excessive fear and anxiety and related behavioral disturbances" (American Psychiatric Association, 2015, p. 1). They are detached from developmental fears, e.g., fear of monsters or the dark, persistent, and lead to a significant decrease in the quality of life (American Psychiatric Association, 2015). Furthermore, anxiety disorders have an early onset and are frequently comorbid with mood disorders, substance abuse, and medical conditions (Harro, 2018). The DSM-5 distinguishes between several types of anxiety disorder and lists diagnostic criteria for each. For instance, generalized anxiety disorder (GAD) is characterized by an inability to control for "repetitive thinking about potential future threats, imagined catastrophes, uncertainties, and risks" (Watkins (2008) as cited in Stevens et al., 2014, p. 378), resulting in worrying covering miscellaneous topics. Apart from the psychological manifestations, the condition is escorted by an extensive amount of stress-related somatic symptoms, e.g., motor tension and behavioral avoidance towards multiple situations, activities, or relationships (American Psychiatric

Association, 2013; Butler et al., 1987). In contrast, specific phobia derives from a fear of phobic stimuli, i.e., an object or a situation (American Psychiatric Association, 2015).

In their overview, Kessler et al. (2012) noted that in adults, the lifetime prevalence of any anxiety disorder was 33.7% in the US, whereas in Germany, the twelve-month prevalence for any anxiety disorder is estimated at 15.3% (Jacobi et al., 2014). Consequently, anxiety disorders are among the most common psychiatric disorder next to mood disorders (Bandelow & Michaelis, 2015; Jacobi et al., 2014; Wittchen et al., 2011). As a result, anxiety disorders and their treatment are one of the biggest challenges in the mental health sector and are subject to extensive research (Kessler et al., 2012; Whiteford et al., 2013).

Unfollowing the traditional categorical approach, newer studies endorse transdiagnostic factors as an explanatory model for developing anxiety disorders, placing them on a dimensional scale. For example, recent findings suggest that the *fear of the unknown* (FOTU) and *intolerance of uncertainty (IU)* play a significant role, along with anxiety sensitivity discussed earlier. Carleton (2016a, p. 5) defines FOTU as "an individual's propensity to experience fear caused by the perceived absence of information at any level of consciousness or point of processing". This definition entails those individuals high in IU develop fear in reaction to the ambiguity and uncertainty of upcoming events (Carleton, 2016a; Carleton, 2016c). In particular, these individuals are biased towards the imagination of worst-case scenarios, whereas low IU persons can endure a certain level of uncertainty regarding upcoming events or situations. As a result, high IU subjects either start to excessively gather information or fall back into a state of avoidance or even freezing-like behavior (Jacoby, 2020). Interestingly, IU was initially developed to explain the worry-component of GAD but soon turned out the be a transdiagnostic vulnerability factor for anxiety disorders and even obsessive-compulsive disorder (OCD) (Buhr & Dugas, 2002; Ladouceur et al., 2000; Sookman & Pinard, 2002; van der Heiden et al., 2010). For instance, Tolin et al. (2003) found that compulsive checkers scored higher on the IU scale than non-checkers. Also, it was observed that the extent of IU distinguishes moderate and severe GAD cases from mild ones (Dugas et al., 2007).

After all, IU seems to be a promising variable in the fundamental understanding of anxiety disorders. For diagnosing personality disorders, the DSM-5 introduced a dimensional approach and thus extended the traditional categorial diagnostical criteria (American Psychiatric Association, 2013). The introduction of a dimensional model for anxiety disorders was also proposed but not put into practice (Knappe et al., 2013; Rabany et al., 2017; Shear et al., 2007). As described earlier, IU is seen as a transdiagnostic factor found in many psychiatric disorders outside of the anxiety spectrum, e.g., autism spectrum (Vasa et al., 2018). Therefore,

IU might provide flexibility within a dimensional approach while simultaneously accounting for the numerous comorbidities that typically occur along with an anxiety disorder (Holaway et al., 2006). At the same time, this concept has not fully gained acceptance yet and lacks a clear distinction from the traditional concepts like trait anxiety or anxiety sensitivity (Birrell et al., 2011; Morriss et al., 2019; Sexton & Dugas, 2009).

Regarding the high prevalence of anxiety disorders, it is surprising that the prevention of these disorders is still not fully understood. Particularly, studies indicate that subthreshold anxiety disorders, i.e., being on a subclinical level close to meeting diagnostic criteria, could be similarly burdensome as a fully developed pathologic condition (Carter et al., 2001; Karsten et al., 2011; Ruscio et al., 2007). Consequently, those affected by it experience a significant psychological burden not only because of their condition but also because they often run under the radar of mental health professionals. What is rather alarming is that in their longitudinal study, Bosman et al. (2019) found out that the prevalence of these conditions is 11.4% in the general population which is relatively high. In addition, they revealed that the symptoms of subthreshold anxiety disorders persisted, and 13.8% of these subjects developed an actual anxiety disorder over the course of three years (Bosman et al., 2019). As this study shows, anxiety disorders often become chronic and develop into the most cost-intensive variable in the mental health sector (Bosman et al., 2019).

Despite recognizing the urgency for intervention, prevention programs for children and adults receive limited support. Also, substantial cost-benefit analyses are still scarce, although proven to be effective despite a few issues that still need to be addressed in further research (Barnett et al., 2021; Bienvenu & Ginsburg, 2007; Domschke et al., 2021). In the sight of all these issues, a dimensional evaluation of anxiety disorders was discussed previously but not considered for the DSM-5 or ICD-11 (Knappe et al., 2013; Shear et al., 2007).

After all, anxiety disorders remain a substantial mental health challenge. Moreover, the "new" concepts of anxiety may set new impulses in not only our fundamental understanding of them but also in creating proactive treatment options.

### 1.2.2 Experimental paradigms

#### *1.2.2.1 Fear Conditioning*

Pavlovian fear conditioning in humans looks back on longstanding traditions. For example, the story of little Albert laid the foundation for the investigation of experimentally invoked fear and its extensive consequences (Watson & Rayner, 1920). While these early tests

may have been controversial, Pavlovian fear conditioning nowadays consists of standardized protocols and significantly contributed to our knowledge of fear and anxiety conceptually, neurobiologically, etiologically, and much more. Consequently, it is an established experimental model for investigating the development and maintenance of pathologic fear and anxiety disorders.

Typically, fear conditioning procedures are oriented to protocols used in animal studies described above (see section **1.1.2.1**) with adaptations to human subjects. For illustrative purposes, Lonsdorf et al. (2017) gave a detailed overview of similarities and differences in humans vs. animal fear conditioning in their review. Equivalent to rodent research, human conditioning studies are segmented into discrete experimental phases, i.e., acquisition, extinction, and test phase, to examine various aspects of fear (Haaker et al., 2019). Furthermore, cues and contexts are usually visually presented on a computer screen or via virtual reality although olfactory and auditory cues can be used but are much more complex to implement (Kastner et al., 2015; Moessnang et al., 2013; Sehlmeyer et al., 2009; Stegmann et al., 2019). For the US, electric shocks applied to a participant's hand or an aversive auditory stimuli, e.g., a loud human scream, are common practice (Scheveneels et al., 2019). The outcome measures cover a wide range of modalities as, in contrast to rodents, subjective data are traditionally collected in humans (Milad et al., 2011). This includes a variety of self-report ratings on fear itself, valence, and expectancy rating of the CS-US association (Haaker et al., 2019; Lonsdorf et al., 2017). In addition, fear is associated with several autonomic responses such as changes in heart rate (variability), electrodermal activity, pupil dilation, brain blood-oxygen level (fMRI), or fear-potentiated startle response, i.e., eye blink (Harrison et al., 2013). Traditionally, behavioral, or cognitive avoidance is also examined (Delgado et al., 2009; Glotzbach et al., 2012).

At present, fear conditioning is somewhat seen as the gold standard in human fear research. Its simple setup allowed the systematic investigation of pathogenic factors of anxiety (Mineka & Zinbarg, 2006). Granted that fear conditioning shares almost identical methods with animal research, this led to an intensive scientific exchange and thus translational advancements. At the same time, fear conditioning is not without controversy. One central point of criticism lies in its transferability to developmental aspects of pathogenesis. For example, in specific phobia, Mowrer’s two-factor theory suggests that phobias are the result of both a classical fear conditioning process, i.e., a former neutral becomes a feared object or situation, and this fear is perpetuated and reinforced by avoidance behavior (operant conditioning) (Antony & Barlow, 1998; Mowrer, 1960). Thus, this model assumes that the development of

this pathology lies in the experience of a traumatic event with the now feared object or situation (Antony & Barlow, 1998). However, most patients cannot recollect such an event (Antony & Barlow, 1998; Spiegel, 2014) – a phenomenon that cannot be explained by fear conditioning yet. In addition, many people might experience traumatic events, yet not everybody develops a specific phobia. Correspondingly, fear conditioning fails to distinguish those at risk of developing an anxiety disorder or not – which is surprisingly paradox about the concept per se (Beckers et al., 2013). In line with this, it is often criticized that most of the work carried out focuses on distinguishing clinical patients and healthy controls, which fails to address vulnerability factors in a non-clinical population (Lissek et al., 2005; Schweckendiek et al., 2011). Moreover, if vulnerability factors are examined, it seems like they often concentrate around physiological parameters, e.g., involvement of brain areas (see Indovina et al., 2011; Klucken et al., 2012 for examples), which adds little to the development of new therapeutical interventions.

#### *1.2.2.2 Behavioral Approach/Avoidance Test (BAT)*

The Behavioral Approach/Avoidance Test (BAT) uses a core element of fear, i.e., avoidance behavior, and translates it to an experimental setting. Initially, it was developed to evaluate systematic desensitization therapy of snake phobia (Lang & Lazovik, 1963). In this, the experimenter asked the subjects to gradually approximate themselves to a cage with a non-poisonous snake following a systematic protocol while simultaneously rating their fear on a "fear thermometer". (Lang & Lazovik, 1963). The distance to the cage was considered a behavioral indicator of fear (Lang & Lazovik, 1963). Furthermore, it was found that the desensitization is reflected in an approach to the cage behaviorally (Lang & Lazovik, 1963). Consequently, the BAT successfully serves as a priori and a posteriori evaluation therapeutic success, is a suitable monitoring tool to examine congruency with subjective fear reports, and can be utilized as a feedback loop for both the therapist and the patient in the treatment of the anxiety disorder (Chorpita & Taylor, 2001). To date, the BAT has been proven valid in a variety of disorders such as OCD (Mancusi & McKay, 2021; Tsao & McKay, 2004), phobias (Miller & Bernstein, 1972; Mühlberger et al., 2008) and even somatic conditions such as back pain (Holzapfel et al., 2016).

Yet what makes the BAT so unique in comparison to other methods? First, the absence of prerequisites, for instance, a conditioning process, is crucial in not contaminating the procedure and its outcome. Therefore, the displayed behavior reflects the response that usually takes place and provides further insights into problematic coping mechanisms that might be critical for therapeutic interventions (Mancusi & McKay, 2021). Additionally, new techniques

like virtual reality (VR) facilitate modeling the features necessary for the BAT and allow designing patient-specific VR scenarios (Mühlberger et al., 2008). Besides, physiological, and self-report measures can easily be incorporated into the BAT procedure.

However, there are a few disadvantages and inconsistencies regarding this test. For instance, it was found that subjects' performance in the BAT is influenced by the therapist's instructions and the individuals' level of fear (Trudel, 1979). Eifert and Duggan (1985) even advocated against the repeated use of the BAT. They assumed that the recurrent and gradual confrontation with the phobic stimulus simulates a graded exposure therapy or even a conditioning process (Eifert & Duggan, 1985). Thus, it does not realistically reflect "natural" avoidance behavior but the result of a learning process, thus compromising subsequent interventions or research approaches (Eifert & Duggan, 1985). Another critical point is the individuality of the BAT. On the one hand, this allows an individualized methodological approach to the subject's fear. On the other hand, it simultaneously complicates comparability across various studies and disorders. Also, this makes the preparation of the test per se complicated as the therapist has to thoroughly elaborate the exact area of concern of the subject beforehand, significantly reducing content validity (Harrington & Antony, 2009).

In sum, the BAT states an instrument to evaluate a patient's behavior in contact with a feared object or a situation. It can provide significant indications of problematic avoidance patterns and aids in finding the appropriate therapeutic strategy. The BAT is a powerful tool in documenting the patient's progress within the therapeutic process. However, the shortcomings mentioned above should not be utilized as the sole assessment tool but rather as a complementary method.

### 1.2.3 Other

#### *1.2.3.1 Subjective Measures*

Subjective measures play a pivotal role in investigating emotions in affective science (Ekman & Davidson, 1994). They allow introspective insights into the subject's cognition, feelings, or opinions and have a significant diagnostic value regarding psychiatric disorders.

Traditionally, self-report data are obtained by standardized rating scales using Likert-type Scales, for instance Subjective Units of Distress Scale (SUDS; Wolpe & Lazarus, 1966). This scale is customarily utilized to rate one's level of fear ranging from 0 (no fear) to 10 or 100 (worst fear ever experienced) within a therapeutical setting to set up a fear hierarchy or for research purposes (Milosevic & McCabe, 2015). On top of that, these Likert-type scales can be

used for various research topics to collect data on attitudes and mental states on an ordinal scale (Brown, 2011). They are easy to be implemented between experimental trials. Another instrument of subjective measures are questionnaires. Usually, questionnaires derive from a theoretical construct, e.g., trait anxiety, and are thoroughly validated and developed to assess this construct's manifestation in individuals systematically. Questionnaires cover a broad range of anxiety, personality, and intelligence testing. Therefore, they are a powerful diagnostic tool in psychological evaluation as they enable a comprehensive account of one individual and throughout larger test samples (Gardhouse & Anderson, 2013).

However, self-report data often fall victim to response biases, such as social desirability, especially if dealing with sensitive topics (Furnham, 1986; Grimm, 2010). Additionally, intellectual or linguistic limitations and introspection ability may distort the outcome and thus reduce the validity of the results (Gardhouse & Anderson, 2013). Also, selecting questionnaires or rating scales requires a careful consideration process on the forehand, so they fit the scientific question. Finally, their processing may be time-consuming and fatiguing for the subject. Still, using ratings and questionnaires is a reasonable and straightforward practice.

#### *1.2.3.2 Objective Measures*

In affective science, objective measurement methods are commonly utilized to examine bodily reflections of emotional states and evaluate their influence and vice versa. In comparison to subjective states, which reflect an individual experience, objective outcome variables are involuntarily generated.

Coming from early emotion theories that state that emotions result from the somatic response, recording brain activity is not that far of a reach (Berkman et al., 2014). In this, electroencephalography (EEG) or functional magnetic resonance imaging (fMRI) are established methods in the observation of central nervous system activity (Quigley et al., 2014). They measure activated brain areas and thus aid in understanding the connectivity of such. This is why we now know that the brain is not an accumulation of isolated entities but a conjoint of interconnected structures (Lindquist et al., 2012). Also, modern affective neuroscience assumes that the amygdala is essential for fear and anxiety and is part of a network that also includes frontal brain areas and structures like the cingulate gyrus (Lang et al., 2000; Saviola et al., 2020). Furthermore, event-related potentials (ERPs) derived from EEG measures allow concluding neural activity in response to events or specific stimuli in real-time (Coan & Allen, 2004; Luck, 2012). Likewise, EEG frequencies are biomarkers for affective disorders themselves (Allen & Reznik, 2015; Haghighi et al., 2017).

Following the theory of Ekman (1992), several studies showed that the activity of particular facial muscles recorded via electromyography (EMG) is linked to discrete emotions (Ekman & Friesen, 1978). Using the facial action coding system (FACS; Ekman & Friesen, 1978), studies pointed out the communicative value of facial expressions and their alteration with regards to mental disorders, emphasizing the importance of facial EMG in affective neuroscience (de Jong et al., 2002; Gavrilescu & Vizireanu, 2019; Schwartz et al., 1976). Another vital application of facial EMG is measuring the fear-potentiated startle blink response in fear conditioning paradigms (Davis et al., 1993; Walker & Davis, 2002).

Measures of the autonomic nervous system represent another vital pillar, and research in physiological changes associated with the experience of emotions has a long history (see Öhman & Wiens, 2003 for further discussion). These records include but are not limited to the examination of heart rate (variability), electrodermal activity (EDA), respiratory rate, pupillary contraction, and hormonal status (Harrison et al., 2013; Wallin, 1981). Concerning fear and stress, it has been established that these biomarkers are connected to the activity of the sympathicus and the parasympathicus, thus being part of the human fight-or-flight response (Gardhouse & Anderson, 2013; Jansen et al., 1995). Over the years, researchers have attempted to evaluate the impact of emotion induction on these physiological domains associated with psychiatric disorders. It has, for instance, been reported that mental disorders are associated with altered cardiac parameters (Boscarino & Chang, 1999; Thayer et al., 1996) and HPA-axis disturbances (Coryell et al., 1989; Staufenbiel et al., 2013; Vreeburg et al., 2010; Young, 2014).

Nevertheless, these techniques often require expensive equipment, apprenticed staff, and advanced statistical skills for data analysis. Therefore, these (budget) limitations are often reflected in a small sample size, which exacerbates the results' generalizations. Also, recording any biological substances or activities is only possible under determined conditions that must be carefully considered. This covers any form of medication, and illegal drug use, as they are known to alter neural, muscular, and autonomic activity (Boisseau et al., 2013; Kirschbaum et al., 1995; Laakmann et al., 1984; Reid et al., 2006). In addition, preexisting conditions such as somatic and mental health issues must be considered and controlled either statistically or methodologically.

After all, the investigation of these biomarkers generates important insights and bridges the gap between the interplay of body and mind.

### 1.2.4 The role of virtual reality (VR) in anxiety research

Virtual reality has received increased attention across a number of disciplines over the recent years. Wiederhold and Bouchard (2014, p.3) defined virtual reality (VR) "[…] as a set of computer technologies, which, when combined, provide an interface to an interactive, computer-generated world." In other words, VR allows the user to immerse fully into a computer-generated environment that still feels like the real world and can interact with it creating a literal human-computer interaction (Jayaram et al., 1997; Myeung-Sook, 2001). Along with the significant price drop of VR soft- and hardware and the increased accessibility, the last two decades have seen a growing trend towards VR application in fear and anxiety research.

Virtual environments (VEs) are usually presented via Head-Mounted-Displays (HMD) or projection screens in a Cave Automatic Virtual Environments (CAVE) (Grimm et al., 2019). An HMD, also called VR glasses, are small displays, whereas a CAVE consists of multiple canvases on which the VR scenario is projected (Grimm et al., 2019). While, on the one hand, HMDs are portable devices and therefore provide flexibility, they, on the other hand, suffer from a restricted field of view, cause dissociation of haptic vs. optical feedback, as the closed HMD system does not allow a visual perception of the own body, and as a result also restrict user's mobility. Alternatively, in the CAVE, the user is surrounded by the virtual world and can walk within the apparatus's dimensions. On the downside, CAVE systems, in contrast to HMDs, are costly regarding purchase and maintenance.

Overall, VR comes along with many major advantages. For example, HMDs are cost-effective, and VEs can be modified effortlessly following the scientific or individuals' therapeutic needs while maintaining complete experimental control of all relevant variables (Bohil et al., 2011; Gregg & Tarrier, 2007; Neo et al., 2021). Moreover, these virtually endless possibilities permit the conduction of experiments that would not be possible in real life, e.g., investigating human spatial memory and navigation using the Morris water task (Driscoll et al., 2005 as cited in Bohil et al., 2011) the virtual human EPM (Biedermann et al., 2017) or even safety behavior in the event of a fire (Kinateder, Ronchi, Gromer, et al., 2014; Kinateder, Ronchi, Nilsson, et al., 2014). Besides, it is also possible to combine VR with self-report feedback and record physiological data in real-time for further insights.

Nevertheless, the construction of VR scenarios and their implementation requires basic to advanced IT knowledge. In addition, the emergence of cybersickness, aka simulator sickness, has to be taken into account. Simulator sickness encompasses several physical symptoms such as sweating, nausea, headache, and disorientation and shares common features with motion

sickness, which is usually experienced when traveling on a ship (Hettinger & Riccio, 1992; LaViola, 2000). As this issue is causing impairment of the applicability of VR, studies identified several risk factors for the development of simulator sickness, i.e., screen size, used device, binocular disruption, navigation control, refresh rate, exposure duration, and latency (Bockelman & Lingum, 2017; Dörner & Steinicke, 2019; Dużmańska et al., 2018; Stauffert et al., 2020). As a result, one of the main challenges faced by VR researchers is the design of VEs that do not elicit simulator sickness but still target the research-relevant domains. This becomes particularly demanding for psychological research as there is a symptom overlap with psychological disorders, e.g., nausea and sweating in acrophobia, which in return might confound data.

Besides, presence is another critical element to accommodate for. The term refers to the feeling of "being" in the situation, although it is virtual and not real (Cummings & Bailenson, 2016; Schwind et al., 2019; Slater et al., 1994). In contrast, the term immersion is associated with the technological aspects of a VR system or scenario, i.e., the level of detail and screen size that create presence (Sanchez-Vives & Slater, 2005). Therefore, a particular concern is to ideally imitate the real world as close as possible, i.e., high immersion and a high presence. It is, therefore, crucial to design a virtual world that abides by the laws of physics and preferably incorporates several sensory channels, as in enhancing the VR scenario with appropriate acoustic and even haptic stimuli if possible (see Peperkorn & Mühlberger, 2013 for an example). Given the ideal conditions, it is then assumed that subjects show the same behavior in VR as they would in the real-world setting (Neo et al., 2021). For instance, Gromer et al. (2018) found that a virtual height scenario effectively elicits fear in acrophobic subjects manifesting in disorder-typical gradual avoidance behavior on an elevated platform.

Nevertheless, virtual exposure therapy (VRET), i.e., the transmission of exposure therapy into a virtual environment, has been established to be an adequate therapeutic tool equally effective or even superior to in vivo exposure (Bouchard et al., 2012; Carl et al., 2019; Krijn et al., 2004; Opriş et al., 2012; Powers & Emmelkamp, 2008). Specifically, VRET has been predominantly used in the treatment of *acrophobia* (Botella et al., 2000; Coelho et al., 2006; Donker et al., 2019), *spider phobia* (Botella et al., 2016; Mühlberger et al., 2008), *social anxiety* (Anderson et al., 2004; Anderson et al., 2003; Dechant et al., 2017) and *fear of flying* (Cardoş et al., 2017; Gregg & Tarrier, 2007). However, VR is not limited to therapeutic approaches of phobias, but is also used for fundamental research such as fear conditioning. For instance, Andreatta et al. (2020) successfully utilized virtual offices for context conditioning protocols and Childs et al. (2017) conducted a VR study to test conditioned place preference.

In sum, VR is a validated and powerful tool investigating of anxiety in humans. Besides its many advantages for behavioral research, it also holds great potential for therapeutic interventions, especially in anxiety disorders.

## 1.3 Translational Research

With new techniques, translational research increasingly gained importance over the last decades (Aragona, 2017). Referring to the Latin word "translatus" meaning "to carry across", translational research is the successive process of deducting practical public (mental) health care implications in a broader sense from basic laboratory scientific findings as in carrying them across from mouse to (wo)men (Drolet & Lorenzi, 2011; Marková, 2018). The "Biomedical Research Translation Continuum" - a five-step model suggested by Drolet and Lorenzi (2011) - defines the translational process as a result of several additive and coherent steps that create a continuous scientific feedback loop. In this, a fundamental scientific discovery, e.g., a psychopharmacological agent, is continuously tested in the laboratory as well as in clinical trials until it is proven effective and safe for human use and can be applied on a broader range in the public health sector (Drolet & Lorenzi, 2011). A historical example of this process is the discovery of the anxiolytic properties of benzodiazepines via animal studies, which led to their establishment as a clinical drug in humans (Wick, 2013). Because of this, benzodiazepines are used as anxiolytic agents, hypnotics, muscle relaxants, and tranquilizers until today (Wick, 2013). Also, identifying and understanding their effect on the central nervous system regarding GABA-ergic activity led to the variety of benzodiazepine-based agents known today (Haefely et al., 1975; Pritchett et al., 1989). Conversely, the knowledge on GABA receptors, their functionality, and specific manipulation via benzodiazepines stimulate the integration of interdisciplinary expertise in the development of novel therapeutic approaches targeting other mental health issues such as autism or schizophrenia (Braat & Kooy, 2015; Rudolph & Knoflach, 2011; Rudolph & Möhler, 2014). Consequently, one can say that translational research not only bridges the gap between various scientific findings but also several disciplines, e.g., biomedicine, psychiatry, and psychology.

In translational research, the implementation of animal models is standard practice. For neuropsychiatric disorders, Nestler and Hyman (2010, p. 1162) demand that they "[…] should derive from plausible risk factors or causative agents […] or else exhibit a substantial degree of neural or behavioral pathology that corresponds convincingly to human disease." Hence, these animal models, specifically rodent models, aim to reflect human psychopathology to experimentally investigate their pathological and often fundamental aspects in a preclinical

stage (Fernando & Robbins, 2011; van der Staay et al., 2009). This approach is advantageous because it permits the implementation of research methods that are impracticable in humans due to ethical reasons. This includes, for instance, lesion studies, genetic modification, and pharmacological interventions and stretches to longitudinal studies that take only a fraction of time in animals. However, it has to be noted that these models only serve as an approximation of pathologies in humans and solely enable examining various aspects of them (Harro, 2018). In preclinical anxiety research, the term "model" fluctuates between the designation of a particular tool or test protocol and altered genetic, developmental, or environmental characteristics that mimic human anxiety and its contributing factors in rodents, which some authors consider problematic (Harro, 2018; Steimer, 2011).

Conclusively, an animal model must meet specific criteria to mimic a condition observed in humans accurately: construct, face, and predictive validity (Belzung & Griebel, 2001; Bourin, 2015; Bourin et al., 2007; Geyer & Markou, 1995; Nestler & Hyman, 2010; Robbins, 2015; Willner, 1991). Firstly, construct validity refers to the "[…] similarity between the theoretical rationale underlying the animal model and the human behavior. This requires that the etiology of the behavior and the biological factors underlying the disorder to be similar in animals and humans." (Bourin, 2015, p. 296). Secondly, face validity includes the notion that the animal model shows a remarkable resemblance with the (pathological) human condition (Belzung & Lemoine, 2011; Goswami et al., 2013). This is, for instance, reflected in the fact that the application of a fear conditioning protocol does induce an observable and measurable fear reaction in the test subject, i.e., in both rodents and humans (Curzon et al., 2009; Lissek et al., 2005; Wotjak, 2019). Finally, predictive validity describes the responsiveness to treatments or pharmacological agents, for example, the decrease of the fear-potentiated startle in mice and humans after the administration of benzodiazepines, due to their anxiolytic properties (Belzung & Lemoine, 2011; Riba et al., 2001; Smith et al., 2011).

In summary, stringent criteria are applied to animal models theoretically. As a result, these guidelines are essential in transferring animal models to humans. The following chapter sheds light on translational approaches and focuses mainly on the paradigms not using conditioning protocols outlined earlier.

### 1.3.1 Overview on Translational Approaches

The more significant part of literature in translational science on fear uses conditioning paradigms to investigate cross-species validity. While this is a delightful scientific development as it consistently revalidates both the paradigm and the results, little if any empirical work has

been done to investigate the cross-species validity of unconditioned rodent behavioral tests. Therefore, there is still uncertainty on whether these tests and even their results are applicable in humans. This especially applies to paradigms like the OFT, the EPM, or the Dark/Light-Box, which are all been part of the quintessential equipment in the rodent lab for decades by now. In this context, one can argue that the BAT already yields conceptual overlap with unconditioned avoidance behavior seen in rodent studies and thus engulfs these methods with a similar outcome. However, the BAT is an exceedingly individualized procedure to adapt to the phobic fears of the human subject. Conversely, in rodent research, the methods mentioned above share at least some grade of standardization across various variables regarding constructional features or exposition time. Also, they typically refer to a state of general anxiety rather than specific phobias. Another obstacle is the replica of the actual test constructions, as they must be adapted to human size. In this case, it cannot be denied that the economic disadvantage outweighs the advantages, as these tests are traditionally preferred because of their effortless setup.

Naturally, the re-translation of animal models intends to find behavioral patterns conserved across species. For example, several studies found that human subjects, in fact, do express thigmotaxis in association with spatial memory (Kallai et al., 2007; Kallai et al., 2005). Other researchers investigated “open field” ambulation in relationship with bipolar mania and schizophrenia and found that both patient groups show a significantly distinct behavioral pattern in the test room (Perry et al., 2009). In addition, they observed that the exploration patterns of bipolar manic subjects share a remarkable overlap with mice deficient in dopamine transporter activity, which is traditionally utilized as an animal model for mania.

Regarding the initial objective of the OFT in investigating parameters in relationship with anxiety, Walz et al. (2016) discovered that agoraphobia and high levels of anxiety sensitivity led to an increase in thigmotaxis in human subjects. Interestingly, anxiety sensitivity is a known risk factor for developing an anxiety disorder (McNally, 2002; Reiss et al., 1986; Schmidt et al., 2006). Consequently, it is even more interesting that the association with thigmotaxis hints at the practicability of the human OFT in uncovering behavioral markers of vulnerability factors before the actual onset of a disorder (Grillon & Ernst, 2016). Unfortunately, newer findings could not replicate the association of thigmotactic tendencies and anxious traits (Gromer et al., 2021). Nevertheless, thigmotaxis, a behavioral index for anxiety previously found in rodents only, remains a constant despite some conceptual drawbacks.

Biedermann et al. (2017) translated the EPM to a mixed virtual reality design and found that, like rodents, humans display a general open arm avoidance. Furthermore, the application

of benzodiazepines led to an increase in time spent on open arms, which is in line with the animal study results of Pellow et al. (1985) and thus insinuates cross-species validity (Biedermann et al., 2017). However, upon further analysis with personality and anxiety traits, open arm activity is substantially associated with acrophobia, i.e., fear of height (Biedermann et al., 2017). However, this paper fails to acknowledge that platform height is not an anxiogenic variable in rodents and that the animal's exploration behavior results from a general disposition (Madeira et al., 2017; Pellow et al., 1985; Treit et al., 1993). Although the mixed reality design, using a real-world wooden cross (30cm width, 20 cm height) for haptics is an innovative approach, it also intensifies the feeling of being in a height situation. In addition, their virtual EPM was positioned 50 meters above virtual water, and the closed arms were "enclosed" by bedrock instead of actual walls (Biedermann et al., 2017). Under these circumstances, it is plausible that enhanced awareness of the height biased their results due to the physical sensation, which might have prompted acrophobia even in non-acrophobic individuals. Per this assumption, some studies found links between fear of falling and a decrease in postural control and security in healthy subjects, which even more, puts the use of the wooden cross for haptics into question (Adkin et al., 2000; Adkin et al., 2002; Davis et al., 2009). Thus, it must be concluded that the validity criteria are not entirely met for this human EPM.

Other translational approaches focus on the induction of an approach-avoidance conflict. While this paradigm refers to traditional rodent tests like the Dark-Light-Box, it is not an exact reproduction of the test situation itself in human translational research. Instead, researchers focus on other methods to better elicit a conflict situation for human subjects. For instance, Aupperle et al. (2011) designed a computer-based task in which the participants were asked to choose between a positive (reward) and a negative (punishment) outcome. Most of the time, this reward was paired with a negative affective stimulus. The authors found that anxiety sensitivity and female gender impact decision-making in this conflict task. Interestingly, this bridges data indicating a higher prevalence of anxiety disorders in women and validates approach-avoidance paradigms to measure general anxiety (Kirlic et al., 2017; Struijs et al., 2017).

Conditioning paradigms are one of the biggest success stories in translational research. So far, animal conditioning protocols could be transferred to humans in an almost 1:1 manner with only minor adjustments. For instance, fear conditioning aided in understanding underlying fear- and memory-related mechanisms of Post-traumatic Stress Disorder (PTSD). Patients with PTSD report intrusive memories, hypervigilance, and persistent negative affect in response to short-term or prolonged exposure to traumatic events or situations (American Psychiatric

Association, 2013). Unlike specific phobia, in PTSD, the triggering and traumatic event can usually be remembered and consciously experienced. Hence, PTSD is understood as the result of real-life fear conditioning. Furthermore, the identification of fear-relevant neurocircuits through animal fear conditioning identified the amygdala and the hippocampal areas as central entities affected by traumatic experiences (Cominski et al., 2014; LeDoux, 1998; Maren, 2001; Yehuda & LeDoux, 2007). Additionally, various studies added the prefrontal cortex to the fear circuit indicating (Koenigs & Grafman, 2009; Kredlow et al., 2022). Based on this, it was confirmed, again via conditioning studies, that PTSD patients suffer from deficiencies in extinction learning and fear-related brain areas are either under- or overactivated in comparison to healthy controls (Milad et al., 2008; Milad et al., 2006; VanElzakker et al., 2014; Wessa & Flor, 2007). Interestingly, extinction deficits along with amygdala, hippocampus and prefrontal cortex anomalies were also found in PTSD-like rats (Goswami et al., 2012; Milad & Quirk, 2012). Consequently, it is now understood that memory and inhibitory deficits perpetuate PTSD and as a result, psychotherapeutic interventions now also emphasize altering post-traumatic impairments instead of relying on exposure therapy only (Foa & McLean, 2016; Holmes et al., 2007; Shubina, 2015).

In summary, translational research plays a vital role in understanding psychiatric disorders on a fundamental level. The cross-species knowledge and method transfer power the scientific communities despite some shortcomings to develop models with the ultimate objective to establish effective treatment options in humans in the first place. Translational research has come a long way, especially regarding fear conditioning. Nevertheless, there are significant scientific gaps regarding frequently used non-conditioning rodent anxiety tests.

## 1.4 The Human Virtual Elevated Plus-Maze

### 1.4.1 Research Objectives

The translation of animal paradigms to humans aims to the cross-species validation of established rodent anxiety tests. Walz et al. (2016) demonstrated that typical fear-related rodent behavioral patterns are evolutionarily conserved in humans and linked to general anxiety traits in the same test used in preclinical rodent research for decades by now. Surprisingly, the (re-)translation of these and other "classic" rodent behavior tests outlined in section **1.1.2.2** have still not yet been extensively performed. This states a rather urgent scientific gap regarding the extensive translational research done on and with fear conditioning. Furthermore, multiple authors addressed the lack of predicational clinical value of these rodent paradigms, which nowadays manifest in a paucity in the development of new anxioselective drugs or interventions

while current treatment options are either insufficient or have side effects, e.g., relapse or addiction (Griebel & Holmes, 2013; Grillon et al., 2019; Sartori & Singewald, 2019). In fact, re-translation, i.e., the development of human paradigms analogous to rodent tests of anxiety, would tremendously help identify etiological and maintaining variables of anxiety (disorders) and boost scientific progress translationally even more. If successful, the generated results could hint at behavioral markers of anxiety disorders before the symptoms manifest on a pathological level. In addition, these studies can also be seen as an attempt to investigate and establish behavioral indices of general anxiety to supplement them to the "traditional" measures.

Therefore, the primary aim of this dissertation is to investigate the cross-species construct validity of the elevated plus-maze in humans. To achieve this goal, human exploration behavior is investigated on a human virtual EPM. Moreover, the particular focus is on evaluating the influence of trait anxiety, a vulnerability factor for anxiety disorders, and its influence on human EPM ambulation over the scope of three experiments. The main objective was to keep the authentic features of the rodent EPM design and protocol to ensure a realistic rodent-human re-translation. Simultaneously, the utilization of VR maintains the economic advantages of the animal test.

Overall, three studies were run to address the previously mentioned research questions and test the hypothesis. Study 1 investigates human exploration behavior and associated psychometric traits using a direct conceptual and constructional transfer of the rodent EPM to virtual reality. Study 2 further investigates human exploratory patterns on the virtual EPM to map out an even more differentiated perspective on the associated anxiety and phobic traits. Finally, Study 3 embeds the EPM to a virtual city environment to test human exploration in a natural and more human-like environment.

### 1.4.2 Hypotheses

This dissertation aims at testing the following hypotheses (Madeira et al., 2021; Madeira et al., 2017):

1) *Humans show a general open-arm-avoidance on the virtual EPM during free exploration.*

Untreated and undrugged rodents avoid the open arms of an EPM instinctively. It is assumed that this behavior is part of their defensive system, presumably to seek shelter from (aerial) predators . Concerning face validity and the existing evidence on evolutionarily conserved

behaviors, e.g., thigmotaxis, it is assumed that this general open arm avoidance is preserved in humans .

2) *Individual's level of trait anxiety influences exploration on the virtual EPM. In this, trait anxiety is positively correlated with open arm avoidance.*

Trait anxiety encompasses an individual's proneness to react more fearful to (potential) threatening or ambiguous situations. This is reflected in (behavioral) avoidance and hypervigilance. Open-arm-avoidance in the rodent EPM is assumed to indicate general anxiety and not phobic fear (see section **1.1.2.5.**). Therefore, the studies presented in this thesis aim to assess the extent to which trait anxiety influences open-arm-avoidance on the virtual EPM, testing translational construct validity .

3) *Open arm avoidance is not associated with acrophobia (fear of height), agoraphobia or claustrophobia.*

Building on the findings that rodent EPM behavior reflects general anxiety, human exploratory activity on the virtual EPM should not derive from phobic fears arising from either platform height, enclosed arms, or the open space on the open arms.

# Studies in Virtual Reality

## 2.1 Study 1: The One-To-One Retranslation

Parts of the following study have already been published as

*Madeira, O., Gromer, D., Latoschik, M. E., & Pauli, P. (2021). Effects of Acrophobic Fear and Trait Anxiety on Human Behavior in a Virtual Elevated Plus-Maze. Frontiers in Virtual Reality, 2, 19. doi: 10.3389/frvir.2021.635048*

### 2.1.1 Introduction

As outlined in section **1.1.2**, behavioral rodent tests play a pivotal role in preclinical anxiety research. Here, non-conditioning paradigms take on particular importance as they are facile and economic in their setup and look back on decades of research (Ohl, 2003). Unlike conditioning studies, these tests do not require prior training or conditioning sessions, thus allowing the observation of natural rodent behavior. However, there exists a scientific paucity in retranslating these commonly used unconditioned anxiety tests to humans which stands in clear contrast to the extensive research conducted on fear conditioning. The very few conducted translation studies revealed remarkable overlaps of rodent and human behavior, for instance thigmotaxis in an OFT (Bach, 2021). Furthermore, distinct exploratory patterns were associated with certain psychopathological conditions (Perry et al., 2009; Young et al., 2016). Over the last years, growing criticism due to the stagnation of the development of new therapeutic approaches for anxiety, put the cross-species validity of these rodent tests into question. Therefore, the systematic retranslation of them aims at the critical analyses of their validity and attempts to generate new insights into human anxiety apart from the results of the rodent studies.

The EPM (see section **1.1.2.5** for further details on the apparatus and test protocol) is a part of the standard rodent anxiety test battery used in preclinical anxiety research and successfully validated anxiolytic and anxiogenic properties of various substances (Pellow et al., 1985). In spite of the EPM's importance in preclinical research, data on a human version of the EPM are still scarce and are not sufficiently convincing (Biedermann et al., 2017). Therefore, the specific objective of this first study was to establish a one-to-one transfer of the rodent EPM to humans and specifically examine the cross-species validity of this apparatus. Owing to the undemanding test setup in rodents, the human EPM was transferred to VR and accordingly adapted in size. Another central point in the investigation is the observation of exploratory

patterns on the platform in an attempt to compare it to rodent ambulation. Finally, the current study is set out to investigate the association of exploratory activity and anxiety traits. Based on the hypotheses, it is expected that, like rodents, humans inherently avoid the open arms, rate them as more anxiety-inducing and that there is a positive association with their level of trait anxiety.

### 2.1.2 Materials and methods

#### *2.1.2.1 Sample and Measures*

The experiment used a student convenience sample of 33 subjects recruited via institute-wide emails and flyers. Due to technical issues during the data record session in the experimental trial, the incomplete data sets of three subjects were excluded from the final analysis ($N$ = 30). The final sample had a mean age of 21.93 ($SD$ = 2.85) years and consisted primarily of women ($N$ = 20). The following inclusion criteria were applied for sample selection: no history of psychiatric disorders, no visual impairments or, if present, corrected via glasses or contact lenses, and no history of epilepsy.

To assess anxiety and personality variables that could influence exploration behavior on the virtual EPM, questionnaires were applied to collect psychometric data. Therefore, to test the second hypothesis, the German version of the *State-Trait-Anxiety Inventory* (STAI; Laux et al., 1981) was used to assess anxious temperament and state anxiety. In addition, the *Anxiety Sensitivity Index* (ASI-3; Kemper et al., 2011) was implemented to account for behavioral aspects of anxiety sensitivity on the virtual EPM. Given the third hypothesis, the *Acrophobia Questionnaire* (AQ; Cohen, 1977) was applied to estimate individuals' level of fear of height as a control variable. In his review, Roberti (2004) pointed out various behavioral characteristics associated with high sensation-seeking levels. This includes but is not limited to high-risk recreational activities, and that sensation seekers tend to approach ambiguous or risky situations with less anxiety (Roberti, 2004; Zuckerman, 1994). Therefore, it was considered that sensation seeking might affect exploratory activity on the virtual EPM and thus added for control. Consequently, the *Sensation-Seeking-Scale Form V* (SSS-V; Beauducel et al., 2003) was implemented. As outlined in section **1.2.4,** virtual reality can elicit somatic effects such as dizziness or nausea. Thus, the *Simulator Sickness Questionnaire* (SSQ; Kennedy et al., 1993) is a self-report questionnaire evaluating somatic side effects of VR exposure. To evaluate the experienced realism and presence, the *Igroup Presence Questionnaire* (IPQ; Schubert et al., 2001) was added.

In addition to the questionnaires, anxiety and presence ratings were integrated right after the exploration trial while in VR as an additional subjective measurement. This was done to gain data on perceived fear and presence simultaneous to virtual exposure. While on the platform, subjects were asked to rate their level of anxiety on one open and one closed arm using Subjective Units of Discomfort Scales (SUDS; Wolpe, 1969) ranging from 0 to 100, respectively. Finally, they were asked to rate their feeling of presence after being asked “To which extent do you feel present in the VE, i.e., as if you were really there?” on a SUDS scale ranging from 0 to 100 (Bouchard et al., 2008).

All participants provided written informed consent and were reimbursed with either 12 € or course credit. Ethical clearance was provided by the Ethics Committee of the Institute of Human-Computer-Interaction of the University of Würzburg. Sample characteristics are displayed in **Table 1.**

**Table 1**. Sample characteristics

| | *N* | *M* | *SD* | *Mdn* | *Min* | *Max* |
|---|---|---|---|---|---|---|
| Age | 30 | 21.93 | 2.85 | 21 | 18 | 30 |
| STAI State T1 | 29 | 34.52 | 6.27 | 35 | 22 | 51 |
| STAI State T2 | 30 | 36.13 | 7.31 | 37 | 23 | 57 |
| STAI Trait | 29 | 34.17 | 6.84 | 34 | 23 | 48 |
| AQ Anxiety | 29 | 18.79 | 15.64 | 14 | 0 | 54 |
| AQ Avoidance | 29 | 3.70 | 3.81 | 3 | 0 | 14 |
| ASI-3 Cognitive | 30 | 4.33 | 4.12 | 3 | 0 | 17 |
| ASI-3 Physical | 30 | 3.63 | 3.66 | 3 | 0 | 16 |
| ASI-3 Social | 30 | 8.00 | 4.74 | 7 | 0 | 18 |
| ASI-3 Total | 30 | 15.97 | 9.98 | 13 | 2 | 42 |
| SSS-V Thrill and Adventure Seeking | 30 | 7.17 | 2.76 | 8 | 0 | 10 |
| SSS-V Disinhibition | 30 | 5.13 | 1.78 | 5 | 1 | 9 |
| SSS-V Experience Seeking | 30 | 7.13 | 1.74 | 7 | 2 | 10 |
| SSS-V Boredom Susceptibility | 30 | 4.10 | 2.00 | 4 | 0 | 8 |
| SSS-V Total | 30 | 23.53 | 6.12 | 25 | 5 | 32 |
| SSQ Nausea | 28 | 1.77 | 1.61 | 1 | 0 | 5 |
| SSQ Oculomotor | 28 | 2.63 | 2.27 | 2 | 0 | 8 |
| SSQ Disorientation | 28 | 2.73 | 2.27 | 2 | 0 | 7 |
| SSQ Total | 28 | 26.75 | 19.74 | 22.50 | 0 | 67.50 |
| IPQ Spatial Presence | 30 | 4.33 | 0.88 | 4.50 | 2.40 | 6 |
| IPQ Involvement | 30 | 3.51 | 0.70 | 3.63 | 2.25 | 4.50 |
| IPQ Experienced Realism | 30 | 2.74 | 0.94 | 2.63 | 1.25 | 5 |
| IPQ General | 30 | 1.83 | 0.87 | 2 | 0 | 4 |
| Rating Anxiety Open Arms | 30 | 17.30 | 20.38 | 10 | 0 | 80 |
| Rating Anxiety Closed Arms | 30 | 4.77 | 6.06 | 3 | 0 | 20 |
| Rating Presence | 30 | 59.37 | 21.20 | 65 | 20 | 95 |

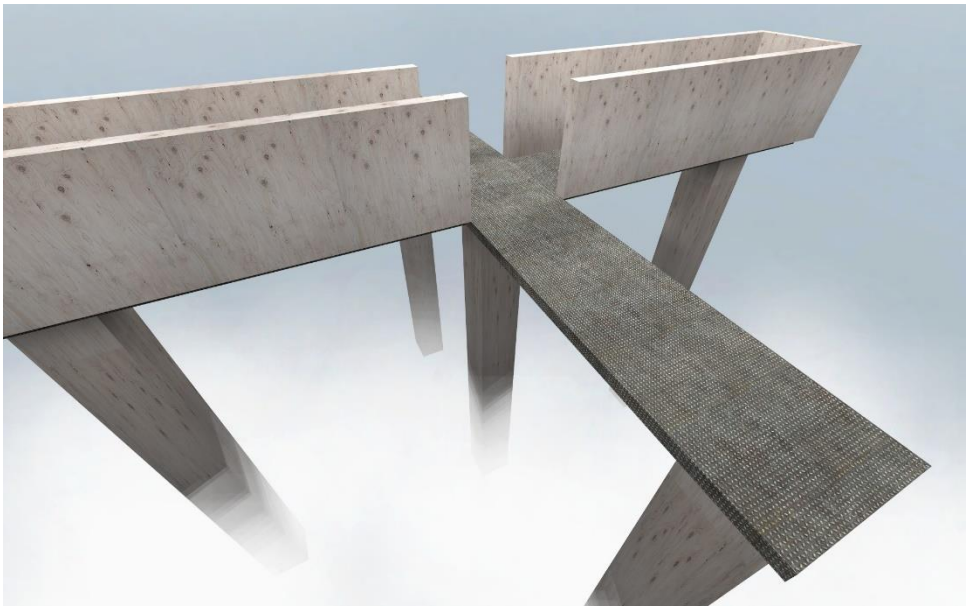
*Note:* STAI = State-Trait Anxiety Inventory (T1 = before the experiment, T2 = after the experiment), AQ = Acrophobia Questionnaire; ASI-3 = Anxiety-Sensitivity Index; SSS-V = Sensation Seeking Scale Form V, SSQ = Simulator Sickness Questionnaire, IPQ = Igroup Presence Questionnaire.

### 2.1.2.2 *Virtual Scenario*

#### *2.1.2.2.1 Virtual Elevated Plus-Maze*

Using a comparative approach, the human virtual elevated plus-maze was adapted one-to-one from the rodent model but modified in size and transferred to virtual reality. Thus, it consisted of four orthogonally arrayed arms, each 11 meters long and 3 meters wide, at the height of ten meters. Wooden-textured walls with a height of three meters enclosed the two closed arms were located opposite each other. The other two arms were open, i.e., without visible barriers; however, transparent walls were implemented to create a physical barrier for safety reasons, e.g., if subjects unintentionally step aside from the platform. Additionally, all arms held an opaque metal floor texture. The platform itself was placed on five wooden-textured pillars, one under each arm and one in the center area to simulate physical laws and not create the impression that the platform "floats". Moreover, the platform was surrounded by a grey and foggy ambient without a visible sun to minimize distracting environmental features that could interfere with exploration behavior (see **Figure 2**). The fog also surrounded pillars to camouflage the height of the platform and to avoid height estimations of the subjects.

**Figure 2.** Screenshot of the human virtual EPM



#### *2.1.2.2.2 Training Level*

Before the experimental trial, implementing a tutorial level is highly recommended to acclimate subjects to the virtual environment (Dörner et al., 2013; Dörner & Steinicke, 2019). Therefore, the completion of a virtual training level was compulsory for all subjects'

participation in the experiment. The training level consisted of a two-floored building with maze-like structures the subjects had to navigate using either the gamepad or their feet. Additionally, all verbal instructions or position markers relevant for the experimental trial and general safety instructions were presented and practiced. From the design aspect, the training level was independent of the virtual EPM, and subjects were given two attempts to finish the level to ensure security in handling the VR environment and the navigation.

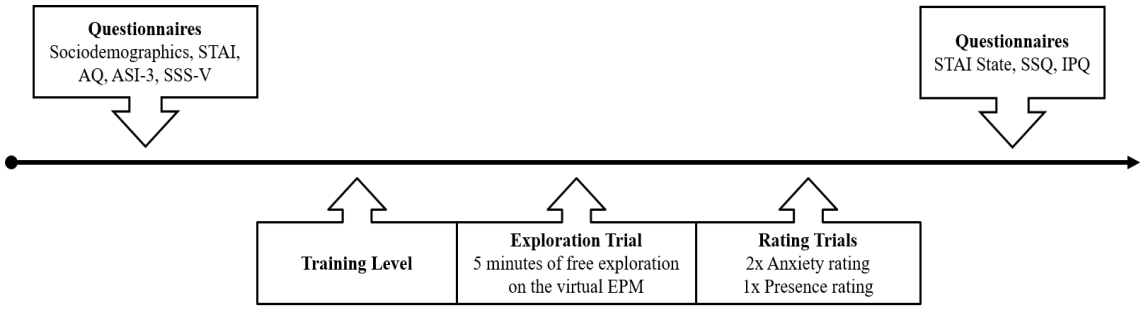
*2.1.2.2.3 Apparatus*

For the presentation of the virtual scenario, a Computer Automatic Virtual Environment (CAVE) sized 4x3x3 meters located in the 3D Multisensoric PsyCave Laboratory of the Department of Psychology I of the University of Würzburg was utilized. Here, the virtual scenario was projected on five canvases (four walls plus floor) via six projectors (NW-7, BARCO, Kuurne, Belgium) with a resolution of 1920x1200 pixels each. Each projector was connected to two computers (Intel Core i7-2600K; 8GB RAM; Nvidia Geforce GTX 580; OCZ Vertex2 SSDs). For motion tracking, four LED infra-red cameras (PhaseSpace Impulse, PhaseSpace Inc., San Leandro, CA, USA) installed on top of the canvases recorded participants' position and rotation. For stereoscopic effect, passive interference-filtering glasses (Infitec Premium, Infitec, Ulm, Germany) were utilized. For navigation over long distances within the virtual scenario, a wireless Xbox 360 controller (Microsoft, Redmond, WA, USA) was implemented, but walking was also possible within the space of the CAVE. For reasons of safety, participants were warned by an acoustic signal if being too closed to the walls.

The virtual scenario was a self-made modification (VrSessionmod 0.6) based on Source Engine SDK 2007 (Valve, Bellevue, Washington, USA) and the CS-Research 5.6 software (VTplus, Würzburg, Germany; see www.cybersession.info for detailed information) managed the experimental procedure.

### *2.1.2.3 Procedure*

**Figure 3.** Schematic representation of the experimental procedure




Prior to data collection, all participants provided written informed consent. Then, subjects completed the first set of questionnaires described in **Figure 3** (Sociodemographics, STAI, AQ, ASI-3, SSS-V). Secondly, after a short safety instruction, the participants were immersed in the virtual training level and were asked to complete it according to the instructions via the CAVE speakers. Failure to complete within two attempts resulted in exclusion. After successfully completing the training trial, the exploration trial was started and ended automatically after five minutes.

Following the exploration trial, the two anxiety ratings were retrieved on one open and one closed arm. The respective platform arm was randomly selected, and the rating sequence was randomized between the subjects. Then, subjects were asked to rate their feeling of presence after the last anxiety rating.

Finally, the second and last set of questionnaires was completed outside of the virtual scenario (STAI State, SSQ, IPQ).

### *2.1.2.4 Tracking Data*

During the exploration trial, the movement of the participants was continuously tracked and recorded via the tracking tools installed in the CAVE. In order to extract data on ambulatory activity, the virtual model of the EPM was divided into three areas, open and closed arms, and center area, by the X and Y coordinates retracted from the positioning data. From these data, the behavioral indices were calculated. These indices included time spent on open and closed arms as well as center area and a minute-to-minute-analyses of time spent in the areas mentioned before. Additionally, walked distance (in meters) is derived from the sum of Euclidean distances and further split based on the positioning data to analyze walked distance on each predefined maze area, i.e., open, closed, center.

#### *2.1.2.5 Data analyses*

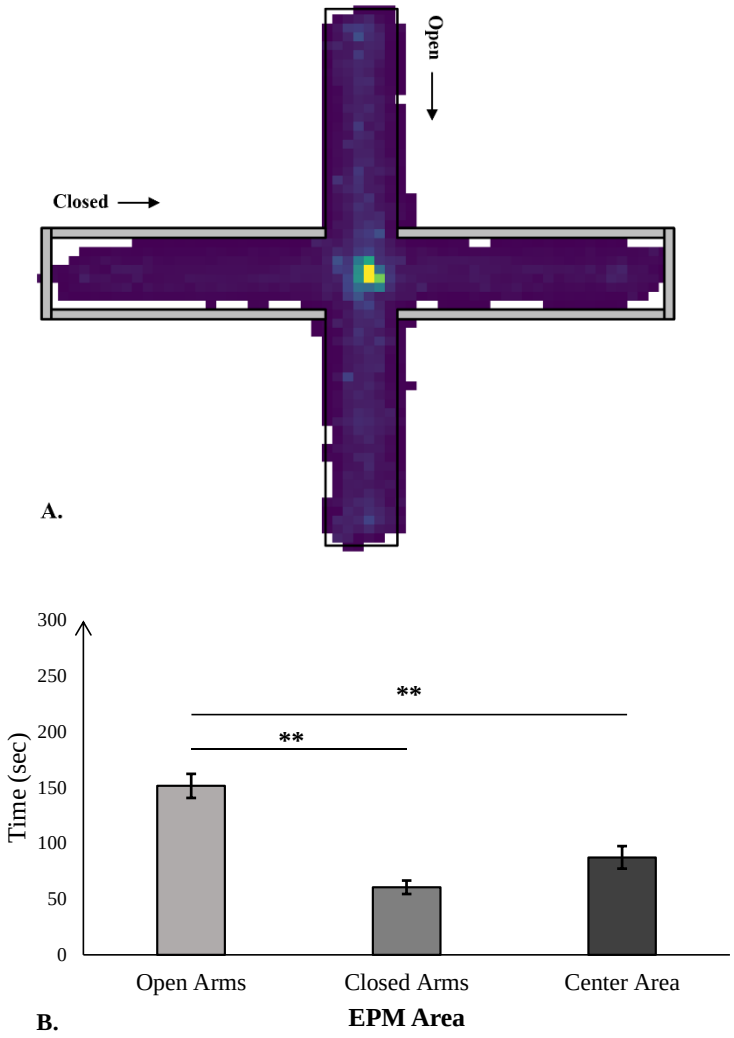
All analyses were carried out using R 3.2.3 (R Core Team, 2013) and SPSS 24 (IBM Corp., 2016). Furthermore, all requirements for statistical test application were computed prior and statistical correction procedures, e.g., Greenhouse-Geisser, Bonferroni, were applied if necessary (Bortz & Schuster, 2010). A $p$ value of $< 0.05$ was considered significant (Bortz & Schuster, 2010).

### 2.1.3 Results

#### *2.1.3.1 Behavioral Data on Exploration Behavior*

Descriptively, subjects spent most of the exploration trial on the open arms of the virtual EPM ($M$ = 151.52, $SD$ = 58.96) followed by the center area in which the participants spent 87.31 ($SD$ = 55.08) seconds on average and finally the closed arms on which participants spent 60.54 seconds ($SD$ = 33.39) (see **Figure 4**). To compare exploratory behavior statistically regarding different maze areas, an analysis of variances (ANOVA) for repeated measures with the three factors open vs. closed vs. center for areas revealed a significant difference in time spent on the EPM areas, $F(43.770, 1.509) = 17.205$, $p < .001$, $\eta^2 = .372$. Bonferroni-corrected post-hoc contrasts showed that subjects spent significantly more time on the open in comparison to the closed arms (90.98, 95%-CI[54.61, 127.36]). Furthermore, the results also revealed that significantly more time was spent on the open arms vs. the center maze area (64.21, 95%-CI[13.60, 114.83]). The difference in time spent on the closed arms and the center area (-26.77, 95%-CI[-58.99, 5.442]) failed to reach significance level.

**Figure 4.** Results of the tracking data during exploration trial.



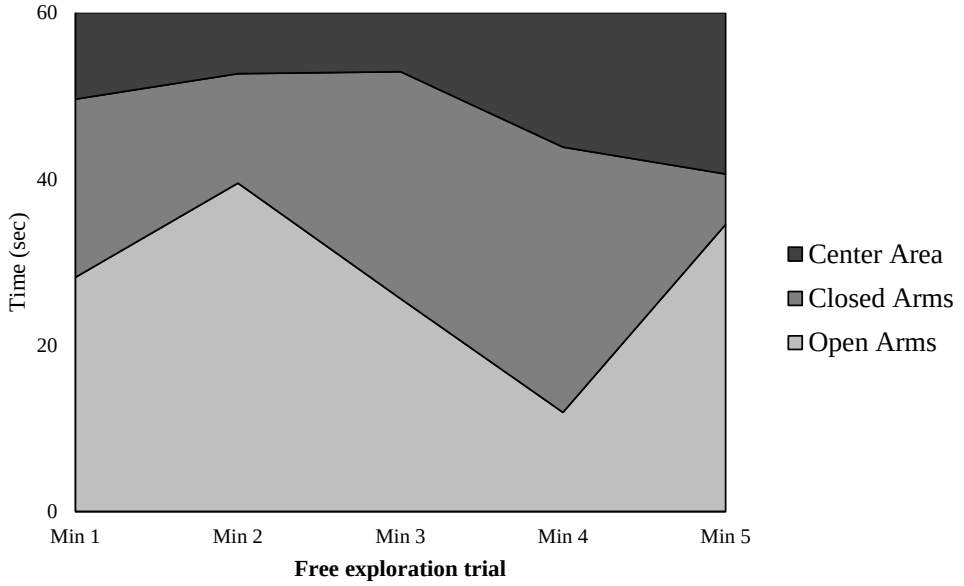

*Note.* **$p < .001$. **A.** Heatmap of motion tracking ($N = 30$). Lighter areas represent areas with more activity. **B.** Overview on time spent on the different area during exploration trial (5 minutes = 300 seconds). The error bars depict the standard error.

Regarding the timeline of exploratory patterns minute-by-minute (see **Figure 5**), it appears that subjects are prone to explore the entire maze but tend to start with the open arms first (minute 1 to minute 2). Over the course of the time, there's a noticeable shift as in increased exploration time spent in the closed arms (minute 2 to minute 4) and finally going back to either the open arms or the center area (minute 4 to minute 5).

Regarding general activity indicated by walked distance on each EPM area, it was found that on average, participants walked 98.15 ($SD = 45.25$) meters on the open arms, whereas they walked less on the closed arms, $M = 51.70$ ($SD = 28.02$), and the center area, $M = 37.03$ ($SD = 8.38$). In total, they walked an average of 191.72 ($SD = 44.85$) meters during the exploration trial. A computed ANOVA for repeated measures revealed that the area specific walked

distances differ significantly from each other (all *ps* < .031). Specifically, this means that subjects were most active on the open arms in comparison to the closed arms and least active on the center area.

**Figure 5.** Temporal exploration behavior over the course of five minutes




### *2.1.3.2 Exploration Behavior and associated traits*

To assess the influence of anxiety and personality traits on exploration behavior according to the second hypothesis a correlation analyses was conducted, and alpha-level was Bonferroni-corrected to $p = .003$.

As can be seen in **Table 2**, for the correlation analysis with the corrected p-level, only the negative correlation between sensation seeking (SSS-V) and time spent on closed arms surpassed significance level. Regarding the uncorrected values, trait anxiety was negatively correlated with open arm activity, $r(27) = -.38$, $p = .043$, however no statistically significant correlation was found for anxiety sensitivity. Secondly, the results hint at a strong influence of acrophobia on open arm avoidance. Accordingly, AQ-Anxiety, $r(27) = -.51$, $p = .005$, and AQ-Avoidance, $r(28) = -.42$, $p = .020$, were negatively correlated with time spent on open arms. In line with this, AQ-Avoidance was also positively associated with time spent on closed arms, $r(28) = .38$, $p = .037$, indicating that participants who tend to avoid height situations in general, also tend to spend more time on the closed arms during the exploration trial. Moreover, there was a positive correlation of AQ-Anxiety and time spent in the center area, $r(27) = .37$, $p = .045$.

Finally, the SSS-V score was also positively associated with open arm activity, which suggests that sensation seekers are more prone to spend time on the open arms during free exploration, $r(28) = .36$, $p = .048$.

**Table 2.** Correlation analyses of trait psychometrics and exploration behavior

| | **Open Arms** | | **Closed Arms** | | **Center Area** | |
|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* |
| STAI-Trait | -.38# | .043 | .17 | .371 | .31 | .105 |
| ASI 3 | -.29 | .119 | .18 | .353 | .20 | .277 |
| AQ Anxiety | -.51# | .005 | .27 | .163 | .37# | .045 |
| AQ Avoidance | -.42# | .020 | .38# | .037 | .22 | .242 |
| SSS-V | .36# | .048 | -.54* | .002 | -.06 | .738 |

*Note. *Bonferroni-corrected* $p < .003$, *#* $p < .05$. $N = 30$. *STAI = State-Trait Anxiety Inventory, ASI-3 = Anxiety Sensitivity Index, AQ = Acrophobia Questionnaire, SSS-V = Sensation Seeking Scale.* Madeira et al. (2021).

Furthermore, a three-step hierarchical regression analysis was performed to narrow down the variables associated with human ambulatory behavior, open arm avoidance specifically, on the virtual EPM. Based on the hypothetical assumptions mentioned in section **1.4.2** and also based on the uncorrected results of the correlational analyses the predictors were consecutively added to the models using time spent on the open arms as dependent variable. Based on the second hypothesis, in the first step trait anxiety (STAI-Trait) was added and in the second step, fear of height (AQ-Anxiety) but not AQ Avoidance score due to high multicollinearity, was included in the analysis. Finally, sensation seeking (SSS-V total score) was subjoined in the third and last step (see **Table 3**). Model comparison revealed that the second model, which includes STAI-Trait and AQ-Anxiety as predictors, best explained open arm activity, $R^2_{adj} = .28$; $F(2, 27) = 6.307$, $p = .006$, $AIC = 303.40$.

**Table 3.** Hierarchical regression analysis on open arm exploration and psychometric traits

| | $R^2$ | AIC | B | SEB | *β* | *p* |
|---|---|---|---|---|---|---|
| *Step 1* | .13 | 319.96 | | | | .033* |
| Intercept | | | 264.64 | 53.03 | | < .001** |
| STAI-Trait | | | -3.43 | 1.53 | -.40 | .033* |
| *Step 2* | .28 | 303.40 | | | | .006* |
| Intercept | | | 258.70 | 48.24 | | < .001** |
| STAI-Trait | | | -2.37 | 1.45 | -.28 | .114 |
| AQ-Anxiety | | | -1.61 | .63 | -.43 | .017* |
| *Step 3* | .26 | 305.29 | | | | .018* |
| Intercept | | | 250.91 | 75.32 | | .003* |
| STAI-Trait | | | -2.36 | 1.48 | -0.28 | 0.158 |
| AQ-Anxiety | | | -1.54 | 0.8 | -0.42 | 0.066 |
| SSS-V | | | 0.28 | 6.38 | 0.03 | 0.892 |

*Note. *p < .05, **p < .001. N = 30. STAI = State-Trait Anxiety Inventory, ASI-3 = Anxiety Sensitivity Index, AQ = Acrophobia Questionnaire, SSS-V = Sensation Seeking Scale.* (Madeira et al., 2021).

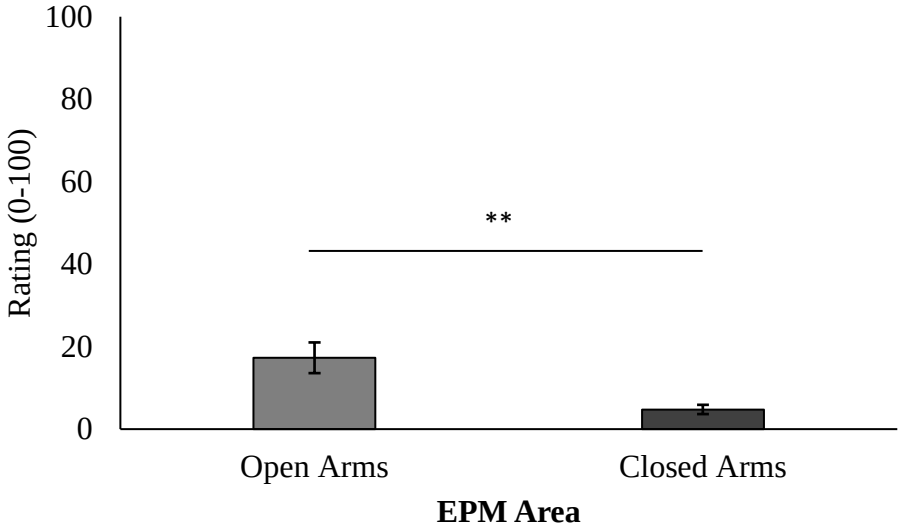
Furthermore, to estimate the influence of the psychometric traits on activity patterns reflected in walking distances on open and closed arms and in the center area, correlational analyses were conducted with a Bonferroni-corrected p-level ($p$ = .003). Results revealed no significant positive or negative association of the walking distances and psychometric traits (all *ps* > .05).

Overall, these results suggest that in contrast to rodents, humans actually prefer the open arms of the virtual EPM, and that open arm avoidance is more linked to acrophobia than to trait anxiety. In addition, the results suggest that there is an association between sensation seeking and EPM ambulation patterns, i.e., closed arm avoidance and open arms approach.

#### *2.1.3.3 Anxiety Ratings*

In general, participants rated the open arms ($M$ = 17.30, $SD$ = 20.38) as more anxiety inducing in comparison to the closed arms ($M$ = 4.77, $SD$ = 6.06) and a t-test for paired samples revealed a significant difference between the two ratings, $t(29) = 3.72$, $p < .001$, $d = 0.68$ (see **Figure 6**).

**Figure 6.** Anxiety rating on open and closed arms.




*Note.* ** $p < .001$, $N$ = 30. The bar plots represent the means of anxiety ratings on the different EPM areas. The error bars depict the standard error.

In order to compare congruency of anxiety ratings with the results of the behavioral data mentioned before, correlation analyses with the traits conducted from the psychometric questionnaires were conducted. Because of repeated testing, the p-value was Bonferroni-corrected to $p = .005$. As can be seen from the **Table 4**, the positive correlations between anxiety ratings on open arms and AQ-Anxiety, $r(27) = .52$, $p = .003$, as well as AQ-Avoidance, $r(28) = .62$, $p < .001$, were significant, respectively. In the context of the results mentioned before, i.e., that acrophobia is the strongest predictor of behavioral open arm avoidance, the results of the anxiety ratings corroborate this suggestion.

For the uncorrected p-value ($p < .05$), the results also suggest a positive relationship between experienced anxiety on closed arms and trait anxiety. Furthermore, a negative

correlation of the SSS-V score with ratings on the open arms was observed, $r(28) = -.47$, $p = .008$.

**Table 4.** Correlation analyses of psychometric traits and anxiety ratings

| | **Anxiety ratings on open arms** | | **Anxiety ratings on closed arms** | |
|---|---|---|---|---|
| | *r* | *p* | *r* | *p* |
| STAI-Trait | .16 | .405 | .42# | .023 |
| ASI-3 | .25 | .181 | .20 | .301 |
| AQ Anxiety | .53* | .003 | .32 | .095 |
| AQ Avoidance | .62* | <.001 | .27 | .156 |
| SSS-V | -.47# | .008 | -.20 | .298 |

*Note. Bonferroni-corrected *p < .005, #p < .05. N = 30. STAI = State-Trait Anxiety Inventory, ASI-3 = Anxiety Sensitivity Index, AQ = Acrophobia Questionnaire, SSS-V = Sensation Seeking Scale. (Madeira et al., 2021).*

#### *2.1.3.4 Correlation of psychometric traits*

Correlational analyses were used to determine the relationship between the psychometric traits estimated via questionnaires. Here it was found that trait anxiety (STAI-Trait) shares a significant positive correlation with the ASI-3 total score, $r(27) = .59$, $p < .001$, indicating a conceptual overlap between the two traits.

Also, acrophobia (AQ-Anxiety) was significantly negatively associated with the SSS-V score, $r(27) = -.61$, $p < .001$ and similar results were observed for avoidance behavior in respect to height situations (AQ-Avoidance) resulting in a significant negative correlation with sensation seeking, $r(28) = -.67$, $p < .001$. These results indicate that sensation seekers are less prone to experience acrophobia and vice versa.

### 2.1.4 Discussion

This study set out to assess cross-species validity and the transferability of the rodent elevated plus-maze to humans. Therefore, an initial objective of this experiment was to assess exploration behavior in the virtual human EPM that resembles rodent exploration, e.g., open arm avoidance and associated anxiety traits.

Concerning the first hypothesis, it was found that humans, unlike rodents, show a general open arms approach rather than avoidance. Also, putting human exploration behavior

into context with the collected data on psychometrics, it was observed that trait anxiety is associated with open arm avoidance at first sight, which supports the second hypothesis and advocates construct validity. However, upon further analysis, it became evident that the association between acrophobia and avoidance of open arms is greater indicating that trait anxiety probably plays a subordinate role. For anxiety sensitivity, no effect was found. Consequently, these results are also in conflict with the third hypothesis, which states that exploration behavior should not be influenced by acrophobia. One unexpected finding was the extent to which sensation seeking influences EPM ambulation, i.e., it is linked to open arm approach and closed arm avoidance.

The results of the anxiety ratings partly mirror the behavioral data. Namely, acrophobia is linked to higher anxiety ratings on open arms, whereas no effect was found for trait anxiety and anxiety sensitivity. In addition, the opposite effect was found for sensation seeking, i.e., lower ratings with increasing levels of sensation seeking.

In their study, Pellow et al. (1985) showed that rodents have a general tendency to avoid the open arms of the EPM and this finding was replicated with a human sample by Biedermann et al. (2017). However, these results significantly differ from the findings presented here. Not only did participants display an open arm approach in general, but also tended to explore them first (see **Figure 5**). In respect to the rodent study, this discrepancy might be attributed to the fact that the high walls of the human virtual EPM might trigger more claustrophobic tendencies leading to feelings of confinement resulting in behavioral avoidance in comparison to Biedermann's human EPM (Biedermann et al., 2017). In line with this assumption, some participants explicitly addressed the narrowness of the closed arms after the experiment. Furthermore, the height of the walls critically obstructs the view over the environment and given that curiosity plays a vital role in exploratory behaviors in higher animals (especially in novel environments) (Dubey & Griffiths, 2020; Silvia, 2017; Spielberger & Starr, 2012), this states a critical limitation. In addition, it can be assumed that the center of the virtual EPM is more of a transition area for arm exploration and thus center (non-)activity appears to be an index of general locomotion.

In this study, high levels of trait anxiety were associated with open arm avoidance, which constitutes the existence of cross-species validity of the EPM and is in line with the hypothesis. However, the more substantial relationship between acrophobia and open arm avoidance fairly surpasses this finding and simultaneously stands in clear contrast to the rodent studies, in which height was not found to be an anxiogenic variable influencing exploration behavior (Martínez et al., 2002; Treit et al., 1993).

A somewhat surprising finding is that subjects generally reported more fear on the open than on the closed arms, which stands in apparent contrast to the general behavioral data. However, a note of caution is due here since, upon detailed inspection, it can be observed that the mean anxiety ratings are relatively low and do not exceed the rating of 20 on a scale ranging from 0 to 100. Furthermore, another closer look reveals that the anxiety ratings share the same associative direction with the behavioral data for acrophobia, but not trait anxiety, i.e., the more acrophobic a participant was, the more fear was experienced on the open arms. Summing up all these findings, they indicate that this virtual EPM does trigger state anxiety that derives from trait anxiety but that the platform height is an even more significant anxiogenic factor that might overshadow the effects of trait anxiety. Therefore, the following study of this dissertation project is required to draw a differentiated picture about the influence of trait anxiety independent of specific phobic traits, especially with the fact that trait anxiety and acrophobia were in this data sample uncorrelated.

Perhaps the most striking but not surprising finding is the compelling influence of sensation seeking on exploration behavior. In the current study, the results suggest that high levels of sensation seeking are linked to closed arm avoidance and the experience of less fear on the open arms, which goes against the general trend of having more fear of them. This finding also replicates those of Biedermann et al. (2017). According to the literature on this topic, sensation seekers are more inclined to exploratory behavior and the approach of potentially phobic situations (Pizam et al., 2001; Zuckerman, 1976).

Nevertheless, there are a few limitations to this investigation that need to be considered. Firstly, with the small sample size consisting of predominantly students, caution must be applied, as the findings might not be generalizable to a broader population. Secondly, the exploration trial with a length of five minutes might have triggered fear habituation that could be a reason for the low anxiety ratings as they were retrieved after the exploration trial. Finally, in transferring the architecture of the rodent EPM to humans enabling direct comparison, numerous participants addressed the artificiality of the virtual environment as such.

Notwithstanding these limitations, the study suggests that there are notable and interesting interactions of human EPM exploration with psychometric traits.

The purpose of the current study was to establish cross-species validity of the EPM by testing the hypotheses that open arm avoidance is conserved translationally in humans and that trait anxiety is associated with it. While this study failed to show general human open arm avoidance, it generated valuable insights into human exploration behavior per se. Furthermore, the results offer a differentiated view on the associated variables influencing human EPM

ambulation although the particular role of trait anxiety independent of acrophobia remains unclear. Therefore, the subsequent study of this dissertation project will examine these links more closely.

## 2.2 Study 2: Re-Designing the EPM

Parts of the following study have already been published as

*Madeira, O., Gromer, D., Latoschik, M. E., & Pauli, P. (2021). Effects of Acrophobic Fear and Trait Anxiety on Human Behavior in a Virtual Elevated Plus-Maze. Frontiers in Virtual Reality, 2, 19. doi: 10.3389/frvir.2021.635048*

### 2.2.1 Introduction

The first study results revealed that in line with the second hypothesis, an association between trait anxiety and open arm avoidance exists indeed, while general open arm avoidance could not be observed. However, this relationship seems to be overpowered by the one with acrophobia reflected in the computed statistical models. Granted that in rodents, height is not considered an anxiogenic variable that influences EPM behavior (Martínez et al., 2002; Treit et al., 1993), this states a critical conceptual mismatch and challenges cross-species validity hypothesized earlier and assumed by Biedermann et al. (2017). In addition, general ambulation patterns revealed a potential influence of claustrophobia triggered by the closed arms of the platform.

Consequently, the ensuing investigation aims at unraveling the effects of trait anxiety on open arm avoidance independent of phobic fears in detail. In order to do so, a few alterations were implemented. In the first place, subjects with low levels of acrophobia were preselected not to reiterate the confounding of the behavioral data, and additionally, a claustrophobia questionnaire was added as a control. Second, design changes were applied to the virtual EPM to manipulate height perception further and adapt the virtual EPM to human use. Specifically, this study introduced various floor textures on different platform parts, either see-through mesh or non-transparent solid floor. Furthermore, the high walls on the closed arms were replaced with standard handrails to, on the one hand, provide a feeling of security without feeling enclosed and on the other hand allow an overlook over the entire virtual environment. Also, arm width was reduced as the arms were considered too wide compared to the animal apparatus. Finally, the sample size was doubled for increased statistical power while the experimental procedure remained the same.

### 2.2.2 Materials and methods

#### *2.2.2.1 Sample and measures*

A total of 68 subjects participated in the experiment and were recruited via institute-wide flyers and online advertisements. They were compensated with either course credit or 12 euros, and the exclusion criteria were equal to those mentioned above. Seven participants were excluded due to technical issues during data acquisition or voluntary abort. The final sample consisted of 61 mostly female individuals ($N$ = 41) with a mean age of 23.21 years ($SD$ = 3.74).

Sample preselection was conducted via an online screening, including filter questions for acrophobia, claustrophobia, and agoraphobia, and estimation of STAI Trait score. To approximately assess the level of acrophobia and in referral to the AQ and its subscales (Cohen, 1977), interested participants were asked to rate their level of fear and avoidance behavior regarding six typical height situations using a five- and three-point Likert Scale, respectively and were invited if they scored 12 points or less on a scale from 6 to 30 on the anxiety scale. For claustrophobia, six items referring to the two subscales (Suffocation, Restriction, three items each) of the CLQ (Radomsky et al., 2001) were to be rated on a five-point Likert scale and participants were also excluded if they scored more than 12 points. Also, the extent of agoraphobic tendencies was assessed asking participants whether they avoid typical agoraphobic situations, i.e., open spaces, after experiencing a panic attack. The presented list of agoraphobic situations derived from the diagnostic criteria for agoraphobia of the ICD-10 (Dilling & Freyberger, 2012) and the occurrence of agoraphobic tendencies stated an exclusion criterion. For the estimation of trait anxiety, a regression model including four items of the STAI-Trait that contributed the most to the explained variance of the sum score was computed (see Stegmann et al., 2019 for further details) but not considered in the selection process.

In order to obtain psychometric data within the virtual laboratory, the identical questionnaire sets used in Study 1 were applied (as described in section **2.1.2.1**). In addition, however, they were complemented with the German version of the Claustrophobia Questionnaire (Radomsky et al., 2001) to control for the influence of fear of enclosed spaces. Analogously, anxiety ratings using the same SUDS range as in Study 1 were conducted; however, ratings took place on all four arms in the current experiment. Again, like Study 1, subjects were asked to rate their feeling of presence.

Ethical approval was obtained from the ethics committee of the Department of Human-Computer-Interaction of the University of Würzburg. Descriptive data of the experimental sample are displayed in **Table 5**.

**Table 5.** Sample characteristics

| | *N* | *M* | *SD* | *Mdn* | *Min* | *Max* |
|---|---|---|---|---|---|---|
| Age | 61 | 23.21 | 3.74 | 23 | 18 | 37 |
| STAI State T1 | 61 | 35.56 | 6.98 | 35 | 20 | 55 |
| STAI State T2 | 61 | 34.74 | 7.25 | 34 | 20 | 52 |
| STAI-Trait | 61 | 37.70 | 9.70 | 37 | 20 | 66 |
| AQ Anxiety | 61 | 17.13 | 12.33 | 14 | 0 | 62 |
| AQ Avoidance | 61 | 3.31 | 2.86 | 3 | 0 | 13 |
| ASI-3 Cognitive | 61 | 3.97 | 3.76 | 3 | 0 | 21 |
| ASI-3 Physical | 61 | 5.87 | 3.97 | 5 | 0 | 17 |
| ASI-3 Social | 61 | 9.84 | 4.85 | 9 | 2 | 22 |
| ASI-3 Total | 61 | 19.67 | 9.29 | 18 | 4 | 45 |
| SSS-V Thrill and Adventure | 61 | 7.03 | 2.17 | 8 | 1 | 10 |
| SSS-V Disinhibition | 61 | 4.56 | 2.07 | 5 | 0 | 10 |
| SSS-V Experience Seeking | 61 | 6.15 | 2.13 | 6 | 2 | 10 |
| SSS-V Boredom Susceptibility | 61 | 3.21 | 1.66 | 3 | 0 | 7 |
| SSS-V Total | 61 | 20.95 | 5.56 | 21 | 9 | 30 |
| CLQ Suffocation | 61 | 6.05 | 4.50 | 5 | 0 | 16 |
| CLQ Restriction | 61 | 13.41 | 8.45 | 12 | 0 | 35 |
| CLQ Total | 61 | 19.90 | 11.73 | 17 | 0 | 48 |
| SSQ Nausea | 61 | 1.66 | 2.08 | 1 | 0 | 11 |
| SSQ Oculomotor | 61 | 2.44 | 2.12 | 2 | 0 | 8 |
| SSQ Disorientation | 61 | 1.95 | 2.31 | 1 | 0 | 10 |
| SSQ-Total | 61 | 22.68 | 20.52 | 18.75 | 0 | 93.75 |
| IPQ Spatial Presence | 61 | 2.86 | .67 | 3 | 1 | 4.20 |
| IPQ Involvement | 61 | 3.50 | .64 | 3.5 | 1.75 | 5.5 |
| IPQ Experienced Realism | 61 | 2.39 | 1.26 | 2 | 0 | 5 |
| IPQ-General | 61 | 2.39 | 1.26 | 2 | 0 | 5 |
| A-Open Grid | 59 | 14.98 | 21.70 | 7 | 0 | 90 |
| A-Open Solid | 60 | 11.92 | 16.38 | 5 | 0 | 70 |
| A-Closed Grid | 58 | 9.72 | 16.93 | 5 | 0 | 80 |
| A-Closed Solid | 60 | 4.13 | 7.73 | 0 | 0 | 50 |
| Presence | 58 | 44.05 | 21.69 | 40 | 10 | 95 |

*Note. STAI = State-Trait Anxiety Inventory (T1 = before the experiment, T2 = after the experiment); AQ = Acrophobia Questionnaire; ASI-3 = Anxiety Sensitivity Index; SSS-V = Sensation Seeking Scale; CLQ = Claustrophobia Questionnaire; SSQ = Simulator Sickness Questionnaire; IPQ = Igroup Presence Questionnaire; A-* = Anxiety Rating.*

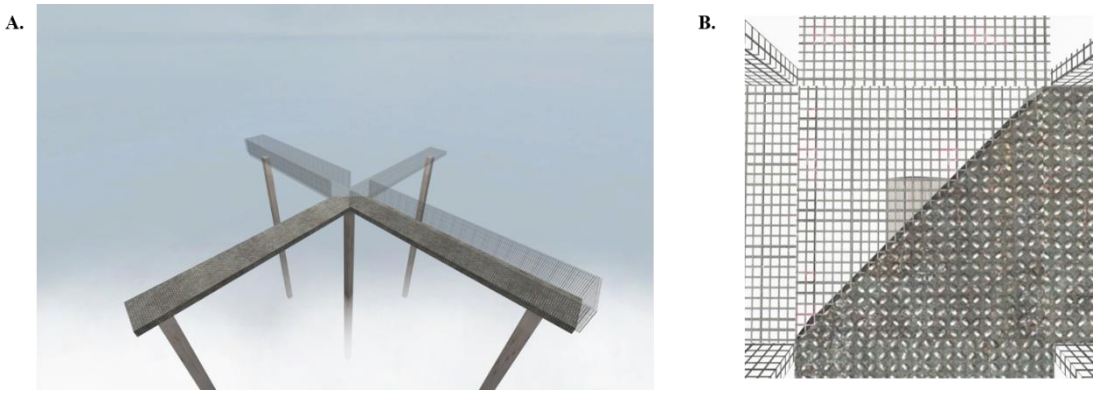
#### *2.2.2.2 Virtual Scenario and Apparatus*

Foundational design aspects of the human virtual EPM were adopted from Study 1 while several details were modified (**Figure 7**). Firstly, there was a reduction of arm width from 3.0 meters to 1.5 meters and arm length from eleven to ten meters. Secondly, floor textures were changed to manipulate height perception. A see-through metal grid floor texture was

implemented on two arms (one open and one closed), whereas the other two arms held the same solid metal floor texture as in Study 1. Meanwhile, the center area incorporated both textures. Finally, the wooden-textured walls on the closed arms were replaced with metal grid textured enclosures at the height of standard handrails (1.3 meters).

The virtual scenario was presented in the same CAVE system described earlier (see section 2.1.2.2.3 for a detailed description).

**Figure 7.** Screenshot of the modified human virtual EPM




**A.** The human virtual EPM with handrails instead of walls on the closed arms and **B.** close-up screenshot of the center area.

### *2.2.2.3 Procedure*

Experimental procedure is mainly equivalent to Study 1. The CLQ (Radomsky et al., 2001)was added to the questionnaire set to be filled out before VR exposure and anxiety ratings were conducted on all four arms to account for the various texture and arm type combinations (grid vs. solid texture, open vs. closed arm).

### *2.2.2.4 Tracking Data*

The tracking data were recorded identically to Study 1 (see section **2.1.2.4** for further details). Also, the retrieved behavioral indices were complimented by adding the participants' first entry choice at the beginning of the exploration trial.

### *2.2.2.5 Data analyses*

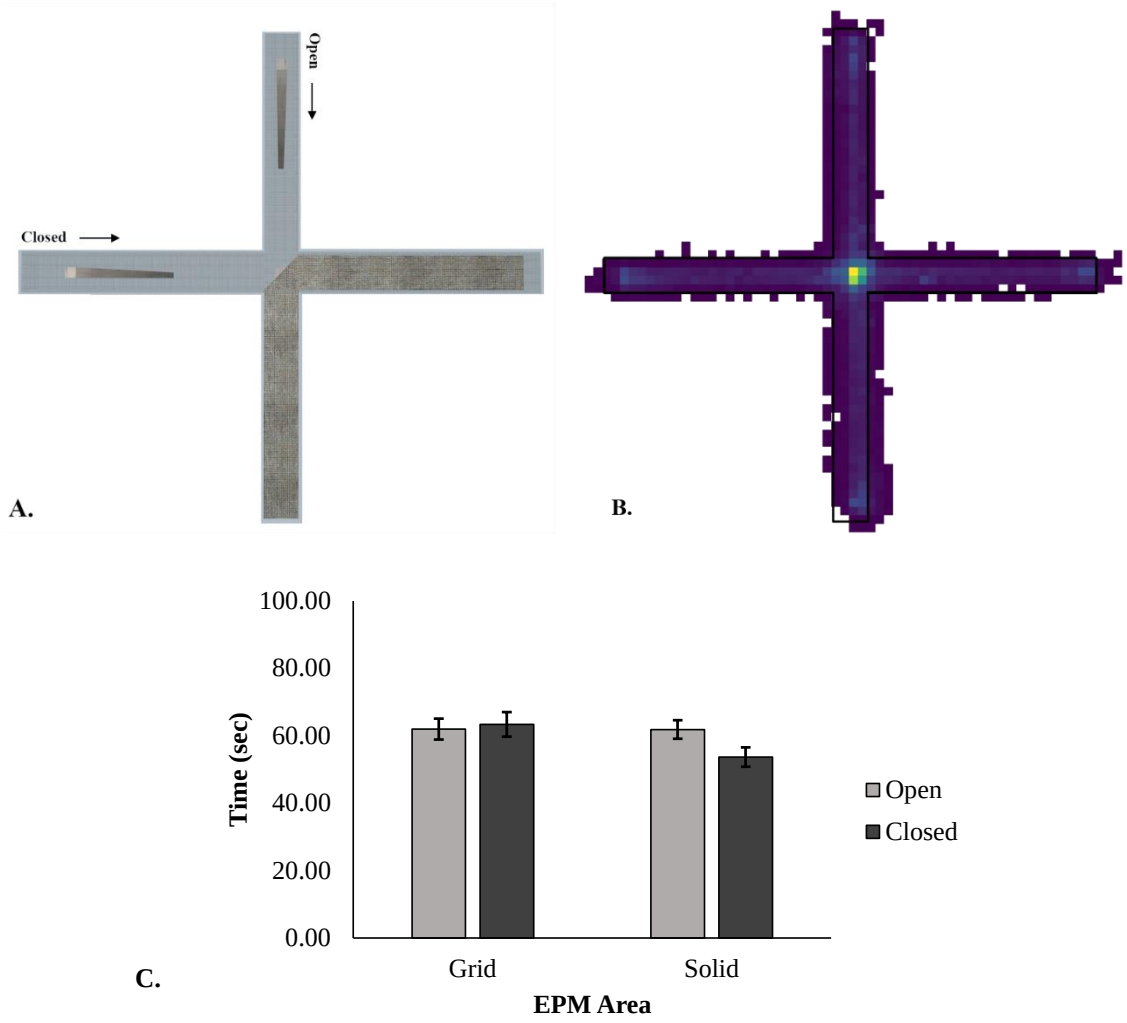
Tools and procedures chosen for statistical testing were identical to Study 1 (see section **2.1.2.5** for further details).

### 2.2.3 Results

#### *2.2.3.1 Behavioral Data on Exploration Behavior*

An analysis of variance (ANOVA) with the within-subject factors arm (open vs. closed) and floor type (grid vs. metal) was conducted to analyze exploration behavior on the virtual EPM and yielded no significant main and interaction effects (all *p*s > .05; see **Figure 8**). Consequently, in this study no general arm preference was observed, which stands in contrast with the results from the first study and the first hypothesis.

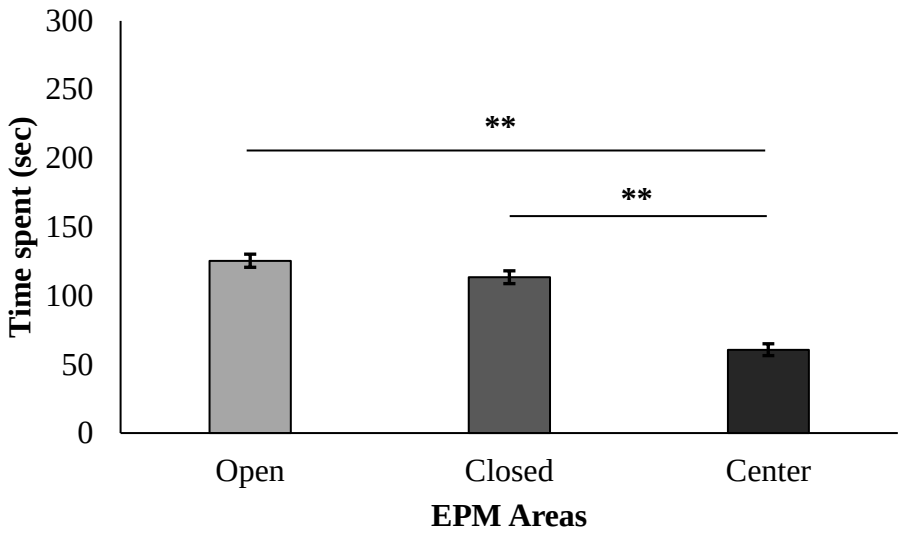
**Figure 8.** Results of tracking data during exploration trial




*Note.* Screenshot of topview (**A.**) and heatmap of exploration behavior (**B.**) on the virtual human EPM. Horizontal arms are closed, and vertical arms are open. Lighter areas depict areas with more activity. The bar plots (**C.**) indicates time spent on the various EPM areas during exploration trial. Error bars depict the standard error. *N* = 61.

To examine EPM ambulation defined as time spent on area irrespective of floor texture, an analysis of variance (ANOVA) for repeated measures with the within-factor area (open arms vs. closed arms vs. center area) was computed and found a significant effect, $F(2, 59) = 41.130$, $p < .001$, $\eta^2 = .58$. This finding indicates that there exists a preference in exploration behavior independent of floor texture. Therefore, t-tests for paired samples with Bonferroni-corrected alpha-level ($p = .017$) were conducted for detailed insights. As shown in **Figure 9,** subjects spend significantly more time on the open arms in comparison to the center area during the exploration trial, $t(60) = 8.16$, $p < .001$, $d = 1.04$. Also, there was a significant difference between time spent on closed arms and center area, $t(60) = 7.30$, $p < .001$, $d = 0.93$, whereas the difference between open and closed arms exploration time failed to reach statistical significance level, $t(60) = 1.49$, $p = .141$, $d = 0.19$.

**Figure 9**. Time spent on the different maze areas during exploration trial




*Note.* $^{**}p < .001$, $N = 61$. Error bars represent the standard error.

The analysis of first entries showed that in 29% of the cases participants entered the closed arm with solid floor first when the exploration trial started. In comparison, 28% explored the open arm with grid or solid floor texture first, respectively, whereas 15% chose the closed arm with grid floor as their first entry. Synthesizing these findings with the general exploration patterns, it can be assumed that also for first entries no clear preferences are visible.

Equivalent to Study 1, the analyses of walked distance were used as an indicator of general activity. On average, subjects walked 44.67 meters ($SD = 16.97$) on the open arm and 47.19 meters ($SD = 18.50$) on the closed with grid floor textures. On the closed arms, the mean walked distances was 44.44 meters ($SD = 18.80$) on the arm with grid floor and 38.65 meters

(*SD* = 15.05) on solid floor. In total, they walked 194.43 meters (SD = 49.89). A repeated-measures ANOVA with the within-factors arm type (open vs. closed) and floor texture (grid vs. solid) revealed a significant main effect for arm type, $F(1,60) = 4.384$, $p = .041$, $\eta^2 = .068$, but not for floor texture. Additionally, a significant interaction effect was found, $F(1,60) = 5.621$, $p = 0.021$, $\eta^2 = 0.086$. Therefore, Bonferroni-corrected post-hoc t-tests for paired samples ($p = .008$) were conducted for detailed insights and only walked distance between open and closed arm with solid floor texture differed significantly, $t(60) = 3.33$, $p = .002$, $d = 0.43$, referring to more activity on the open arm.

#### *2.2.3.2 Exploration Behavior and associated traits*

Correlation analyses using Bonferroni-corrected alpha, $p = .002$, were performed to assess the associations between psychometric traits and exploration behavior. The results show a significant negative relationship between time spent on open arm with grid floor texture and the AQ subscale "Avoidance" ($r(59) = -.40$, $p = .001$) signifying those subjects who tend to avoid height situations, also spent less time on the most "acrophobic" EPM arm. For non-corrected values, the results also hint at a negative association of open grid arm activity and fear of height (AQ Anxiety), $r(59) = -.36$, $p = .004$. Also, there was a positive relationship between STAI-Trait and time spent on the open arm with see-through grid floor, $r(59) = .29$, $p = .021$. In view of the results of the first study that showed a relationship in the opposite direction, this finding is rather surprising. Other correlations were not significant. The results of the correlational analyses are summarized in **Table 6**.

**Table 6.** Correlational analyses of psychometric traits and time spent on EPM arms

| | **Closed grid** | | **Closed solid** | | **Open grid** | | **Open solid** | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| STAI-Trait | -.25 | .050 | -.10 | .463 | .29# | .021 | .08 | .548 |
| ASI-3 | -.12 | .364 | -.11 | .419 | .05 | .677 | -.06 | 659 |
| AQ Anxiety | .02 | .863 | .15 | .253 | -.36# | .004 | -.12 | .377 |
| AQ Avoidance | .04 | .768 | -.02 | .859 | -.40* | .001 | .02 | .877 |
| SSS-V | -.19 | .150 | -.09 | .492 | -.13 | .328 | .06 | .656 |
| CLQ | .04 | .773 | -.05 | .717 | -.08 | .539 | -.06 | .633 |

*Note. *Bonferroni-corrected $p < .002$, #$p < .05$. N = 61. STAI = State-Trait Anxiety Inventory, ASI-3 = Anxiety Sensitivity Index, AQ = Acrophobia Questionnaire, SSS-V = Sensation Seeking Scale, CLQ = Claustrophobia Questionnaire. (Madeira et al., 2021).*

Relating to results of Study 1, correlational analyses with Bonferroni-adjusted p-value ($p$ = .002) were also conducted explore the influence of psychometric traits on EPM exploration behavior irrespective of floor texture. As displayed in **Table 7** there were no significant results whereas for uncorrected p-values only the negative association between AQ-Anxiety and time spent on the open arms, $r(59)$ = -.33, $p$ = .009, and AQ-Avoidance and time spent on the open arms, $r(59)$ = -.30, $p$ = .019. In addition, there was also a positive correlation of SSS-V score and center area activity, $r(59)$ = .26, $p$ = .047. Notably, the relationship between acrophobia and open arm avoidance corroborates the results of Study 1 and emphases the importance of fear of height on EPM exploration.

**Table 7.** Correlation analyses psychometrics with exploration behavior

| | **Open** | | **Closed** | | **Center** | |
|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* |
| STAI-Trait | .20 | .122 | -.21 | .113 | -.01 | .917 |
| ASI-3 | .00 | .977 | -.09 | .504 | .08 | .523 |
| AQ-Anxiety | -.33[#] | .009 | .19 | .134 | .17 | .195 |
| AQ-Avoidance | -.30[#] | .019 | .10 | .452 | .23 | .069 |
| SSS-V | -.01 | .948 | -.24 | .060 | .26[#] | .047 |
| CLQ | -.10 | .466 | .07 | .567 | .03 | .814 |

*Note. *Bonferroni-corrected p < .003, [#]p < .05. N = 61. STAI = State-Trait Anxiety Inventory, ASI-3 = Anxiety Sensitivity Index, AQ = Acrophobia Questionnaire, SSS-V = Sensation Seeking Scale, CLQ = Claustrophobia Questionnaire.*

Based on the uncorrected results of the correlational analyses, the findings in Study 1 and in view of the hypothesis mentioned earlier, a four-step hierarchical regression analysis was calculated to determine the influence of the various psychometric traits on time spent on the open arms. In the first step, trait anxiety was added to the model. In the second step, fear of height (AQ-Anxiety) but not height associated avoidance behavior (AQ-Avoidance) was included. In the next step, sensation seeking was added in and in the fourth and final step, claustrophobia (CLQ) was added. From the data shown in **Table 8**, it can be assumed that based on $AIC$ = 610.67, and adjusted $R^2$ = .16, the second linear regression model including STAI Trait and AQ Anxiety best explained open arm activity, $F(2, 58) = 5.346$, $p$ = .007. Here, the direction of the estimation parameters points to a greater influence of acrophobia on open arm avoidance than trait anxiety, which corroborates the findings of Study 1.

**Table 8.** Hierarchical regression analyses on open arm exploration and psychometric data

| | ***R2*** | ***AIC*** | ***B*** | ***SEB*** | ***β*** | ***p*** |
|---|---|---|---|---|---|---|
| *Step 1* | .04 | 616.50 | | | | .122 |
| Intercept | | | 96.62 | 18.99 | | <.001** |
| STAI Trait | | | .77 | .49 | .20 | .122 |
| *Step 2* | .16 | 610.67 | | | | .007* |
| Intercept | | | 111.83 | 18.76 | | <.001** |
| STAI Trait | | | .83 | .46 | .22 | .079 |
| AQ Anxiety | | | -1.03 | .36 | -.34 | .007* |
| *Step 3* | .11 | 612.56 | | | | .002* |
| Intercept | | | 118.74 | 28.87 | | <.001** |
| STAI Trait | | | .80 | .47 | .21 | .095 |
| AQ Anxiety | | | -1.05 | .37 | -.35 | .007* |
| SSS-V | | | -.27 | .84 | -.27 | .753 |
| *Step 4* | .10 | 614.52 | | | | .006* |
| Intercept | | | 116.93 | 30.90 | | <.001** |
| STAI Trait | | | .80 | .48 | .21 | .098 |
| AQ Anxiety | | | -1.07 | .40 | -.36 | .010* |
| SSS-V | | | -.023 | .87 | -.04 | .791 |
| CLQ | | | -.08 | .43 | .02 | .862 |

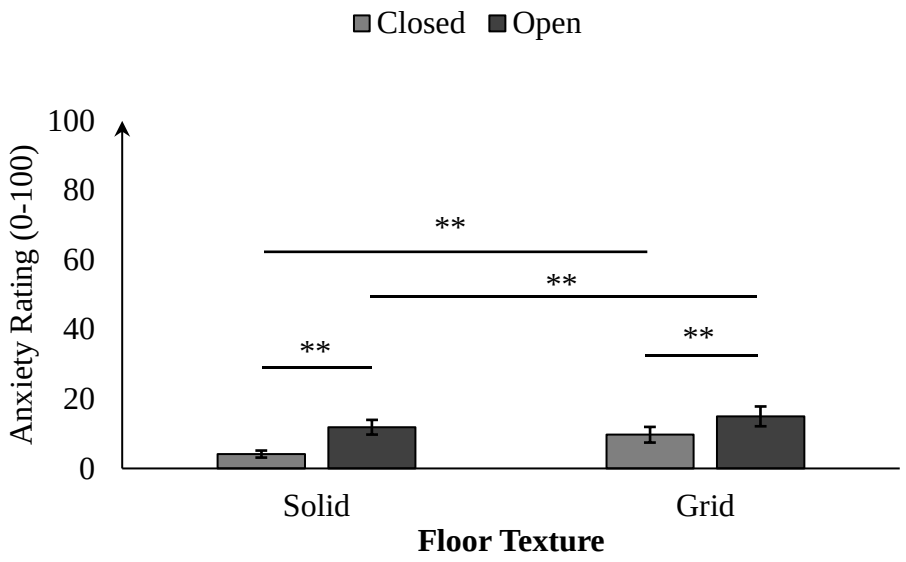
*Note. *p < .05, **p < .001. N = 61. $R^2$ = adjusted $R^2$. STAI = State-Trait Anxiety Inventory, ASI-3 = Anxiety Sensitivity Index, AQ = Acrophobia Questionnaire, SSS-V = Sensation Seeking Scale, CLQ = Claustrophobia Questionnaire. (Madeira et al., 2021).*

Summing up, the results on exploration behavior suggest that no general arm preference in human EPM ambulation is observable. However, taken together with psychometric data there is a robust association of open arm avoidance and acrophobia but not trait anxiety. Interestingly, the importance of fear of height influencing EPM behavior is strongly reflected in the avoidance of open arm with grid floor, which also represents the EPM area with the best height perception.

### *2.2.3.3 Anxiety Ratings*

To reveal differences in anxiety ratings on the various virtual EPM areas, a 2x2 ANOVA for repeated measures with the within-subject factors arm type, open vs. closed, and floor texture, grid vs. solid, was calculated. The results revealed significant main effects for arm type, $F(1,56) = 27.61$, $p < .001$, $\eta^2 = .33$ and floor texture, $F(1,56) = 12.33$, $p = .001$, $\eta^2 = .18$, but no significant interaction effect, $F(1,55) = .33$, $p = .569$, $\eta^2 = .06$ . The results obtained from the post-hoc t-tests with Bonferroni-corrected p-value ($p = .008$) show significant differences in anxiety ratings between open arms with grid and solid floor ($t(56) = 4.46$, $p < .001$, $d = 0.59$) and closed arms with grid and solid floor, $t(56) = -3.10$, $p = .003$, $d = -0.41$. Also, the ratings differed significantly regarding arm type, as in open vs closed arms with solid floor, $t(58) = 5.09$, $p < .001$, $d = 0.66$ and open vs. closed arm with grid floor, $t(56) = 4.46$, $p < .001$, $d = 0.59$. Finally, anxiety ratings between open arm with grid floor and closed arm with solid floor also differed significantly, $t(58) = 4.90$, $p < .001$, $d = 0.64$ whereas the difference between open solid and closed grid arms failed to reach significance level, $t(57) = 1.98$, $p = .053$, $d = 0.26$. To sum it up, the findings show that generally open as well as grid-floored arms were rated as more anxiety inducing in comparison to closed arms or arms with solid floor texture, respectively (see **Figure 10).**

**Figure 10.** Anxiety ratings on closed and open arms




*Note.* $*p < .05$, $**p < .001$, $N = 61$.The error bars represent the standard error.

In addition, correlation analyses with Bonferroni-corrected *p*-value ($p = .002$) were performed to evaluate the associations of anxiety ratings and psychometric traits. As can be seen in **Table 9**, there were significant positive correlations between AQ Anxiety as well as AQ Avoidance and anxiety ratings on all arms (all *p*s < .001) but the closed arm with solid floor, which also represents the safest one from an acrophobic point of view. Additionally, significant negative associations were found between sensation seeking (SSS-V) and anxiety ratings on the closed arm with grid floor, $r(56) = -.43$, $p < .001$, and the open arm with solid floor, $r(58) = -.45$, $p < .001$. Hence, these findings underline the importance of the influence of sensation seeking on human EPM behavior. Moreover, there were significant positive relationships between the CLQ-score and anxiety ratings on all arms (all *p*s < .001). This is a rather surprising finding, as it is rather unspecific and does not hint at an explicit direction on the influence of claustrophobia and anxiety experienced on the virtual EPM. Furthermore, no statistically significant correlations were observed for trait anxiety (STAI-Trait) or anxiety sensitivity (ASI-3), $p > .055$.

**Table 9.** Correlation analyses of psychometrics and anxiety ratings

| | **Closed grid** | | **Closed solid** | | **Open grid** | | **Open solid** | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| STAI-Trait | .05 | .712 | .18 | .171 | .01 | .921 | .13 | .309 |
| ASI-3 | .14 | .298 | .25 | .055 | .16 | .229 | .17 | .202 |
| AQ Anxiety | .57* | <.001 | .36# | .004 | .49* | <.001 | .49* | <.001 |
| AQ Avoidance | .46* | <.001 | .34# | .008 | .51* | <.001 | .50* | <.001 |
| SSS-V | -.43* | <.001 | -.38# | .002 | -.38# | .003 | -.45* | <.001 |
| CLQ | .45* | <.001 | .42* | <.001 | .43* | <.001 | .45* | <.001 |

*Note. Bonferroni-corrected *p < .002, #p < .05. N = 61. STAI = State-Trait Anxiety Inventory, ASI-3 = Anxiety Sensitivity Index, AQ = Acrophobia Questionnaire, SSS-V = Sensation Seeking Scale, CLQ = Claustrophobia Questionnaire.*

#### *2.2.3.4 Correlation of psychometric traits*

In order to estimate the relations of the used psychometric traits with each other, questionnaire intercorrelations were calculated. The results as displayed in **Table 10** revealed significant positive correlations between trait anxiety and anxiety sensitivity, $r(59) = .64$, $p < .001$, replicating the findings of study 1. Also, the CLQ total score and both AQ subscales (Anxiety: $r(59) = .48$, $p < .001$; Avoidance: $r(59) = .43$, $p < .001$) were positively correlated

whereas the CLQ score, and sensation seeking were negatively associated, $r(59) = -.28$, $p = .028$.

**Table 10.** Intercorrelations of psychometric questionnaires

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| 1. STAI Trait | — | | | | | |
| 2. ASI-3 | .64** | — | | | | |
| 3. AQ Anxiety | .05 | .22 | — | | | |
| 4. AQ Avoidance | .12 | .16 | .58** | — | | |
| 5. SSS-V | -.18 | -.08 | -.20 | -.25 | — | |
| 6. CLQ | .05 | .25 | .39** | .48** | -.28* | — |

*Note. **p < .001, *p < .05. STAI = State-Trait Anxiety Inventory, ASI-3 = Anxiety Sensitivity Index, AQ = Acrophobia Questionnaire, SSS-V = Sensation Seeking Scale, CLQ = Claustrophobia Questionnaire. N = 61.*

### 2.2.4 Discussion

In continuation of the first study, the present experiment was designed to examine human exploration behavior on the virtual EPM and further assess associated traits that influence it to establish cross-species validity based on the previously mentioned hypothesis. In particular, design adaptations of the apparatus itself and sample preselection aimed at improving the differentiation of the separate influence of trait anxiety and acrophobia, respectively.

Contrary to the first hypothesis, no open arm avoidance and even no general arm preference was observed. In this connection, the observation of first entries also did not provide any indications on exploratory preferences in EPM ambulation, which is inconsistent with the findings of Study 1 and the ones of Biedermann et al. (2017). Moreover, the analyses of walking distances as an indicator of general activity suggest more activity on open arms with solid floor texture. Again, regression analyses identified acrophobia but not trait anxiety as the primary variable in open arm avoidance, corroborating Study 1 and Biedermann et al. (2017). In addition, the most notable finding of fear of height and exploratory patterns is that the displayed avoidance behavior is most pronounced on the open arm with the grid-textured floor, i.e., the one that triggers fear of heights the most, underlining the acrophobic potential of the virtual EPM. For trait anxiety, the results hint at the opposite direction, as contrary to the findings in

Study 1 and the second hypothesis that it is associated with open arm approach. This is unexpected and suggests that trait anxiety presumably only plays a subordinate if any role in EPM exploration. No effects were observed for anxiety sensitivity, sensation seeking, and claustrophobia.

A closer look at the anxiety ratings reveals that the most "acrophobic" EPM areas, i.e., open, and grid-floored arms, trigger higher fear ratings. In line with this, mirroring behavioral results, again, fear of height is strongest linked to the ratings, i.e., the more acrophobia, the more fear is experienced on the EPM arms but the close one with solid floor texture. Along with the behavioral data, this finding only confirms the impact of acrophobia. Surprisingly, all fear ratings were also negatively correlated with claustrophobia but are presumably the result of the CAVE design, which probably triggers claustrophobic fear. In contrast, sensation seekers tend to experience less anxiety on the EPM whereas no effects were found for trait anxiety and anxiety sensitivity.

This study investigated human ambulation patterns on the EPM in concordance with the rodent model to validate the EPM. In light of the first hypothesis, the results of the current study combined with those of the first one suggest that humans, unlike rodents, display no distinct arm preference or avoidance on the virtual EPM during free exploration. Again, this finding contradicts the findings of Biedermann et al. (2017), who were able to reproduce rodent-like open arm avoidance in humans. However, based on the findings on the outcomes of both studies, it is very likely that the factors discussed earlier might bias their data (see **2.1.4** for details).

In line with this, the iteration of the lack of a general open arm avoidance states an important consistency that questions cross-species validity of EPM behavior claimed by Biedermann and colleagues (2017) even more. Given that the sample was screened to exclude high levels of acrophobia beforehand, this finding is even more compelling. Here, it has to be noted that the AQ does not provide a cutoff value for clinical levels of fear of height. However, studies using a clinically acrophobic sample usually report AQ Anxiety scores of at least 55 or more (Baker et al., 1973; Cohen, 1977; Emmelkamp et al., 2002; Powers & Emmelkamp, 2008). In the current study, the mean score is 17.13 on the Anxiety subscale although the range suggests an outlier with a sum score of 62 (see **Table 5**). However, the results of an exploratory analysis excluding this subject did not change the actual results found before (see Appendix).

Nevertheless, how is it possible to observe acrophobia-typical behavior in the non-acrophobic sample on the virtual EPM? This finding may be explained by the fact that height represents a potentially life-threatening danger from a Darwinian point of view (Blanchard et

al., 1989). Following the preparedness theory[3] of Seligman (1971), fear of heights and the associated avoidance behavior is an evolutionary predisposed feature as it protects the individual from sudden death by falling (Blanchard et al., 1989; Coelho et al., 2009; Marks & Nesse, 1994; Öhman & Mineka, 2001). Consequently, this would also explain why most people experience levels of "discomfort" at least if exposed to height situations (which is also reflected in the AQ Anxiety scores that are indeed low but also not close to zero in the current sample) and the rather high prevalence rates of acrophobia per se (Huppert et al., 2013; Huppert et al., 2020; Kapfhammer et al., 2015). Summing up these findings and taking them together with those of Biedermann et al. (2017) it is very likely that the platform height of the virtual EPM becomes the most salient feature and triggers the height-associated discomfort mentioned before. However, this theory does not fully explain why this is not observable in general exploratory activity, e.g., a general avoidance of open arms. Supposedly, this could be since subjects' acrophobia did not range within clinically significant levels in both studies. As a result, it can be assumed that general exploration behavior is merely shaped by the design of the virtual EPM and not necessarily the psychometric structure of individuals walking on the platform.

Regarding the anxiety ratings, the results indicate that they did not exceed an average of a score of 15 out of 100, which is very low again. This replicates the findings of Study 1 and supports the assumption that this version of the virtual EPM is not an anxiogenic environment per se but solely triggers anxiety in association with already present phobic-related fears. Consequently, this can be observed in the elevated rating scores for the grid floored and the open arms, which hint at the continuous influence of acrophobia on EPM behavior and experience. Also, sensation seeking was associated with experiencing less anxiety on the maze. This corroborates the findings of Study 1 and points to the importance of sensation seeking. Surprisingly, claustrophobic tendencies were also linked to more anxiety irrespective of arm or floor type. However, these results may be an artifact of the research apparatus. Granted that the CAVE is masked by the virtual scenario during the exploration trial, before each of the ratings, there was a fade-out that presumably interrupted immersion and might have triggered the awareness of the CAVE as an enclosed space. Under those circumstances, it is not surprising that this might have elicited claustrophobic fear even though subjects' claustrophobia levels

[3]Seligman (1971) theorized that humans carry a genetic and biological disposition to acquire fear reactions to those objects and situations more quickly, which pose a risk to survival (McNally, 1987).

were on a non-clinical level. Consequently, future studies need to consider the possible bias in these responses and create VR scenarios or experimental procedures to avoid them.

Having a look at questionnaire intercorrelations yielded a few interesting insights. Again, trait anxiety (STAI Trait) was positively correlated with anxiety sensitivity (ASI-3), whereas both questionnaires remained unassociated with the AQ and other psychometric tools. Surprisingly, claustrophobia (CLQ) was positively correlated with both AQ subscales and negatively associated with sensation seeking (SSS-V). Here, the link between CLQ and AQ is not surprising, as according to the DSM-5, 75% of individuals with specific phobia also develop more than one fear (American Psychiatric Association, 2015). Taken that the current study used a non-clinical sample, it is remarkable that this correlation is present at all. Additionally, a closer look at the intercorrelations revealed that sensation seeking marginally and negatively correlates with AQ Avoidance ($p$ = .055). In Study 1, there was a robust and significant negative correlation of these data. Hence, an exploratory correlation analysis was conducted of both AQ subscales and all SSS-V subscales. Here, it was found that this association primarily stems from the significant negative correlation of the AQ subscales and the SSS-V subscale “Thrill and Adventure Seeking”. Upon closer inspection of the subscale items, it was noted that this subscale contains items that query behavioral tendencies in height situations and therefore strongly resemble the AQ items. For this reason, this observed correlation has to be taken with a grain of salt, as it might be biased, given the self-reported nature of the two questionnaires together with this conceptual overlap.

Several participants mentioned the artificiality of the virtual environment. In particular, subjects disapproved of the lack of visual and acoustic enrichment, especially the given exploration task. In this context, some of the tested individuals stated that they felt uncomfortable with freely exploring the virtual environment without an obvious task attached to it. While one on the one hand, one could argue that this insecurity of events might trigger high trait anxious individuals, the relatively low anxiety ratings mark that this virtual scenario did not provoke feelings of anxiety at all. Presumably, this might refer to being in an unrealistic and not promptly threatening environment. Taken together with the also rather low presence ratings (on average 45 out of 100), these results are also in line with findings on the associations between presence and experienced fear in virtual scenarios, e.g., Gromer et al. (2019) who found that fear leads to an increase in feelings of presence. Thus, future virtual studies using a human EPM should work towards a more naturalistic outline of the environment and enrich it with corresponding sound effects and visual features that simultaneously do not affect natural exploration while at the same time encouraging exploratory activity. This might be put into

effect by a virtual scenario that humans already experienced as an exploratory environment, e.g., a museum, or by introducing them to a task. Inevitably, future studies need to break away from the rather artificial model of the rodent EPM. Additionally, even though sample size was increased to improve statistical power, this current study uses a sample of convenience. Thus, these results may not be generalizable to a broader population.

In summary, in this investigation, the aim was to assess cross-species validity of the rodent EPM by a virtual human EPM by finding corresponding evolutionary conserved exploration patterns such as a general open arm avoidance. Also, the main goal of the current study was to adapt this apparatus to humans, e.g., by lowering closed arm wall to handrail level and to further evaluate the effects of trait anxiety on exploration behavior independent through variations in floor textures. Combining the inconsistent results on trait anxiety in both studies and returning to the hypotheses, it is now possible to state, that this virtual human EPM measures behavioral aspects of acrophobia but not trait anxiety. The findings also clearly indicate that humans show no general open arm avoidance challenging cross-species validity claimed by Biedermann et al. (2017) once more. So far, all the proposed hypotheses remain unconfirmed as it seems like the height of the platform overpowers all other possible other explanation models or variables.

## 2.3 Study 3: The City EPM

### 2.3.1 Introduction

Based on the findings of the studies above, this experiment was conducted to improve the scenario per se and to account for numerous issues. Furthermore, results of both previous studies suggested acrophobia as the primary variable of open arm avoidance. As this interferes with the initial objective of testing exploration behavior in association with trait anxiety, this maze aimed to eliminate the height situation to have a further look into the influence of anxiety and personality traits on exploration behavior. With a view on the low anxiety ratings in the previous two studies, an arousal rating was added also included for further insights.

Also, the virtual scenario was enriched by adding ambient sound and incorporating the EPM into a city environment to create a more naturalistic environment and initiate explorative behavior more subtle. Additionally, the release of novel equipment for VR scenarios and software introduced a more economical and improved way of designing and conducting virtual studies. In contrast to the two studies conducted before, an HMD instead of a CAVE system was utilized to allow this study to be more convenient and economical.

### 2.3.2 Materials and methods

#### *2.3.2.1 Sample and measures*

The study sample was preselected based on the online screening described in section **2.2.2.1.** However, for this study the estimated trait anxiety score was included in the selection process, i.e., potential study subjects were included if estimated STAI Trait Score was either $\leq 33$ for a low trait anxious group and $\geq 41$ for the high trait anxious group. Additionally, subjects were asked to be free of claustrophobic and agoraphobic symptoms. All participants provided written informed consent prior to study participation.

After recruitment via flyers and through an online platform, 67 subjects were invited for data collection. Ten participants were excluded due to either majorly overstepping the navigation area or issues with the navigation equipment per se. On average, the mostly female ($N = 35$) participants were 25.09 (SD = 6.45) years old and predominantly students ($N = 46$). The study participation was either compensated with 8 Euros or course credit.

For psychometrics, almost the identical questionnaires were implemented. However, as this virtual scenario did not include height, the AQ (Cohen, 1977) was dismissed. In addition, an arousal rating was implemented after each anxiety rating. There, subjects were asked to rate

their arousal level ("How arousing do you rate the environment?" "Wie aufregend finden Sie die Umgebung?") using SUDS on scale from 0 to 100 (Wolpe, 1969).

Sample characteristics are provided in **Table 11**.

**Table 11.** Sample Characteristics

| | *N* | *M* | *SD* | *Mdn* | *Min* | *Max* |
|---|---|---|---|---|---|---|
| Age | 57 | 25.09 | 6.45 | 24 | 18 | 51 |
| STAI State T1 | 57 | 31.96 | 5.96 | 32 | 20 | 47 |
| STAI State T2 | 57 | 31.44 | 7.78 | 32 | 19 | 54 |
| STAI Trait | 57 | 36.74 | 10.49 | 35 | 20 | 63 |
| ASI-3 Cognitive | 57 | 4.09 | 3.80 | 4 | 0 | 16 |
| ASI-3 Physical | 57 | 4.02 | 3.50 | 3 | 0 | 14 |
| ASI-3 Social | 57 | 8.40 | 4.34 | 8 | 1 | 18 |
| ASI-3 Total | 57 | 16.51 | 9.05 | 17 | 1 | 44 |
| SSS-V Thrill and Adventure Seeking | 57 | 6.98 | 2.14 | 8 | 0 | 10 |
| SSS-V Disinhibition | 57 | 4.47 | 2.65 | 4 | 0 | 16 |
| SSS-V Experience Seeking | 57 | 6.51 | 1.98 | 7 | 2 | 10 |
| SSS-V Boredom Susceptibility | 57 | 2.86 | 1.73 | 3 | 0 | 7 |
| SSS-V Total | 57 | 20.82 | 6.02 | 22 | 4 | 40 |
| CLQ Suffocation | 57 | 5.04 | 4.88 | 4 | 0 | 27 |
| CLQ Restriction | 57 | 9.18 | 7.58 | 8 | 0 | 33 |
| CLQ Total | 57 | 14.21 | 11.10 | 13 | 0 | 60 |
| SSQ Nausea | 57 | 1.32 | 1.47 | 2 | 0 | 7 |
| SSQ Oculomotor | 57 | 2.28 | 2.38 | 2 | 0 | 11 |
| SSQ Disorientation | 57 | 1.56 | 1.68 | 1 | 0 | 6 |
| SSQ-Total | 57 | 19.34 | 18.57 | 15 | 0 | 82.50 |
| IPQ Spatial Presence | 57 | 3.67 | 0.41 | 3.6 | 3 | 4.60 |
| IPQ Involvement | 57 | 4.74 | 0.40 | 4.75 | 4 | 5.50 |
| IPQ Experienced Realism | 57 | 3.98 | 0.60 | 3.75 | 2.50 | 5.25 |
| IPQ General | 57 | 1.61 | 0.98 | 2 | 0 | 4 |
| Anxiety Open | 57 | 3.81 | 8.97 | 0 | 0 | 50 |
| Anxiety Closed | 57 | 7.57 | 12.18 | 1 | 0 | 60 |
| Arousal Open | 57 | 28.36 | 22.40 | 20 | 0 | 75 |
| Arousal Closed | 57 | 32.61 | 22.40 | 30 | 0 | 80 |
| Presence | 57 | 62.89 | 21.11 | 70 | 15 | 95 |

*Note. STAI = State-Trait Anxiety* Inventory *(T1 = before the experiment, T2 = after the experiment); ASI-3 = Anxiety Sensitivity Index; SSS-V = Sensation Seeking Scale; CLQ = Claustrophobia Questionnaire; SSQ = Simulator Sickness Questionnaire; IPQ = Igroup Presence Questionnaire.*

### *2.3.2.2 Virtual scenario and apparatus*

#### *2.3.2.2.1 City EPM*

The virtual scenario consisted of a plus-shaped intersection scene within a city environment with four dead-end roads. Each of the four orthogonally aligned streets included a sidewalk and an asphalted street. The navigation area was restricted to the asphalted roads, which were 65 meters long and 9 meters wide, to standardize the walking area across all participants and avoid non-maze ambulation. The two open arms resembled an open city park area covered with lawn. Conifer and broadleaf trees were used to cover the horizon at the end of each open arm. Additionally, all implemented plants were animated to blow in the wind to ensure a naturalistic and realistic setting. On the other hand, the closed alleys were flanked by houses with shop facades in resemblance to the closed arms of the rodent EPM (see **Figure 11**).

**Figure 11.** Screenshot of two arms of the City EPM

The left maze alley displays one of the closed arms whereas the right arm is one of the two open arms. The yellow lines represent the preset navigation area. Fire hydrants (invisible during exploration trial) mark the position for the anxiety, arousal, and presence ratings.

Oversized fire hydrants were positioned at about two-thirds on all four arms and had green footprints in front of them to tag the desired position for the participants in order to rate anxiety, arousal, and presence. However, the fire hydrants and the footprints were faded out during the exploration phase. The hydrants were implemented as an additional visual aid, as in pilot studies, it was found that the green footprints alone were not visible from the starting point

(center area), and therefore subjects were unsure on how to follow the instruction to go forward for their rating. Additionally, ambient background sound was implemented to enrich the virtual environment acoustically. In doing so, the sounds alternate depending on the arm type. For the open arms, the looped ambient sound simulated a city park scenery with chirping birds, the rustling of the wind and car noises in the background, whereas for the closed arms the acoustics resembled a typical city traffic scene. For both sceneries, the sounds were selected not to include any human voices to avoid the influence of social clues on exploration behavior. To ensure a smooth transition between the two sound types, sound cones oriented at dimensions of the alleys were implemented and overlapped in the center area.

*2.3.2.2.2 Training level*

The training level consisted of a two-floored building with a labyrinth-like array of walls. This level was included for participants to master navigation with the HTC Vive Controller and familiarize themselves with virtual reality, auditory instructions, and navigation assets. The subjects' objective was to find a pulsating sphere on the second floor and simultaneously represent the level end. In addition, ambient white noise was incorporated to enhance immersion and block sounds from outside. Participants were given a maximum of two trials to finish the training level and were excluded from further testing if unsuccessful.

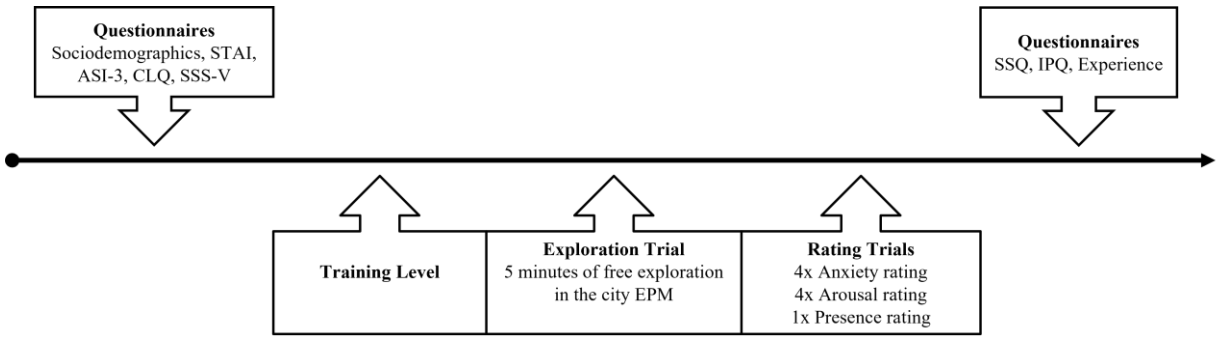
*2.3.2.2.3 Apparatus*

The virtual scenario was presented via the head-mounted display HTC Vive Pro (HTC, New Taipei City, Taiwan) on a Dual AMOLED 3.5" diagonal screen with a resolution of 1440 x 1600 pixels per eye (equals 2880 x 1600 pixels combined) and a refresh rate of 90 Hz connected to one computer (Intel Core i7-2600k, 16 GB RAM, Samsung Evo 850 SSD, Nvidia Geforce 970 GTX). Auditory elements of the virtual scenario, such as instructions and background noises, were presented via attached HTC Vive Deluxe Audio Strap. In addition, the Steam VR Tracking System of the HTC Vive with two tracking base stations were used to track participants rotation and position. One of the two HTC Vive Controllers was used for navigation within the virtual environment and subjects were able to move along the maze via a self-setup teleport system by pressing the Trigger button of the HTC Vive controller. Here, the maximum teleport distance was set to two meters to avoid unrealistically big jumps within the maze and the future position was indicated by a white hexagon if the controller was pointed to the ground. In addition, walking by foot was possible within approximately 2.5m x 3.5 meters and the SteamVR Chaperone system notified subjects if they came to close to the preset space boundaries (cf. Gromer et al., 2021).

The virtual scenario and the experimental procedure were constructed with Unreal Engine 4.14 (Epic Games, Cary, North Carolina, USA) and the utilized assets were retrieved from the “Showdown Demo”, “Kite Demo” and “Open World Demo Collection”.

#### *2.3.2.3 Procedure*

**Figure 12.** Experimental procedure of Study 3




STAI = State-Trait-Anxiety Inventory, ASI-3 = Anxiety Sensitivity Inventory, CLQ = Claustrophobia Questionnaire, SSS-V = Sensation Seeking Scale Form V, SSQ = Simulator Sickness Questionnaire, IPQ = Igroup Presence Questionnaire

The experimental procedure (see **Figure 12**) was based on the rodent animal studies and the human studies described above. At first, participants filled out the first questionnaire set (Sociodemographics, STAI, ASI-3, CLQ, SSS-V) followed by the virtual training level. After completing the training trial, subjects had five minutes to freely explore the city maze from the center area until the rating trials started. To avoid bias, the starting gaze direction was randomized across all participants for the exploration trial. The rating trials included anxiety and arousal ratings on all arms, i.e., eight ratings in total and one presence rating after the last arousal rating was completed. For the rating trials, the subjects were teleported to the center area and were then asked to go forward to the now faded-in hydrant with the green footprints on one of the arms. Here, the sequence of the rated arms was randomized across all subjects as well. After completing the rating trials, the participants were taken out of the virtual environment and filled out the second set of questionnaires (SSQ, IPQ, VR Experience).

#### *2.3.2.4 Tracking Data*

Position of subjects was tracked continuously during the exploration trial. Here, a text file writer was implemented into Unreal Engine 4 to extract the virtual player position with a sample rate of 20 Hz (see https://github.com/dgromer/ue4-misc/blob/6581653cdacbd1b63e883c992c2207e1157b2d39/LogFileWriter/4.20/LogfileWriter.cpp for details). To extract data on movement behavior, the virtual model of the EPM was divided into three areas (open and closed arms, center area) by the X and Y coordinates obtained from the text file with the positioning data and the model built in Unreal Engine 4. The calculated behavioral indices used for the analyses were identical to the ones used in study 1 and 2.

#### *2.3.2.5 Statistical Analyses*

See section **2.1.2.5** for further details on statistical analyses.

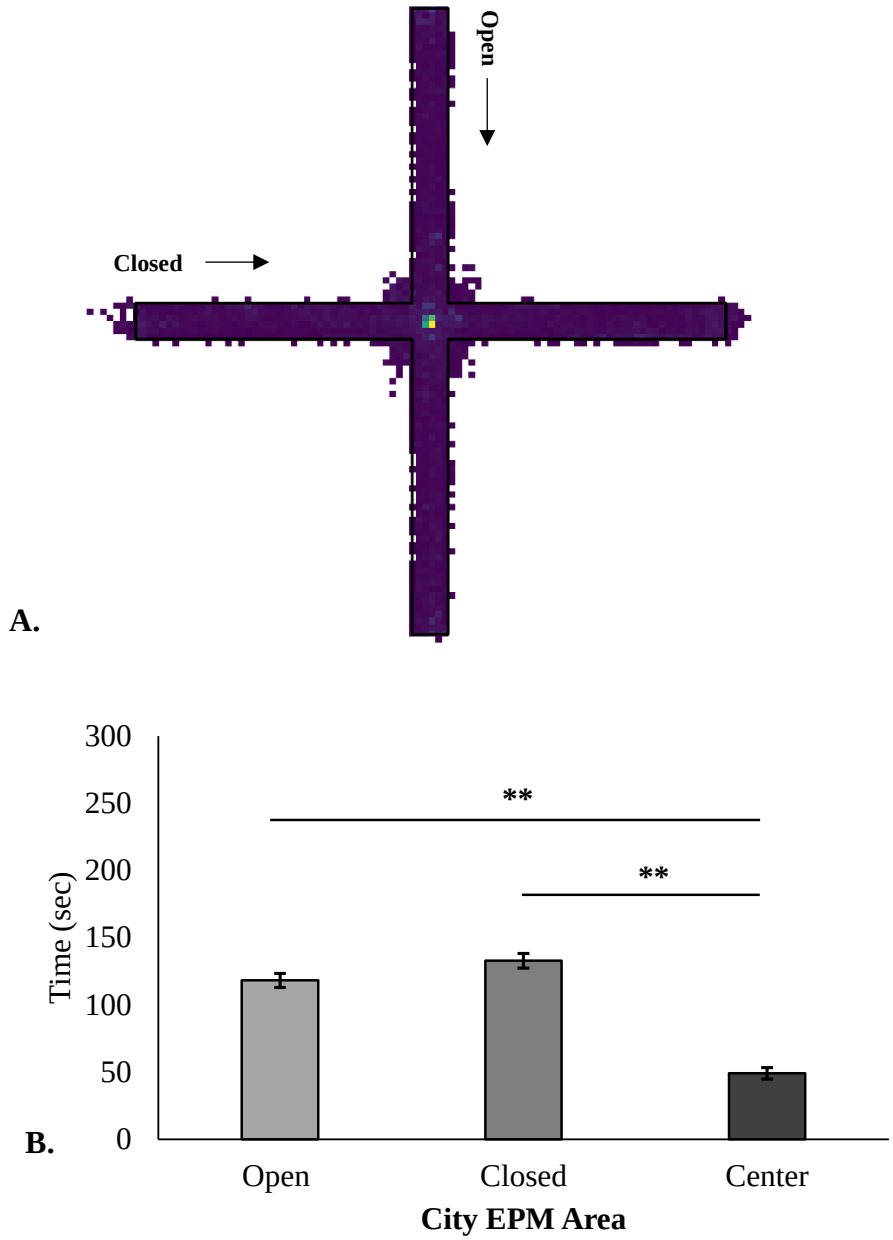
### 2.3.3 Results

#### *2.3.3.1 Behavioral Data on Exploration Behavior*

A descriptive analysis of the exploration data showed, that on average participants spent the most time on the closed arms, $M = 132.78$, $SD = 40.81$, followed by the open arms, $M = 118.22$, $SD = 39.58$, and spent least time in the center area, $M = 49.01$, $SD = 32.63$.

To compare the mean scores, ANOVA for repeated measures with three between factors, open vs. closed vs. center, was computed and revealed a significant effect between the three conditions, $F(2,112) = 53.147$, $p < .001$, $\eta^2 = .487$. Therefore, Bonferroni-adjusted post-hoc tests were calculated and showed significant differences ($p < .001$) between time spent in open arms and center area (69.21, 95%-CI[49.61, 88.82]) as well as time spent on the closed arms and center area (83.77, 95%-CI[63.37, 104.17]). The difference between time spent on open and closed arms failed to reach significance level, $p = .421$ (see **Figure 13**).

**Figure 13.** Results of tracking data during the exploration trial




*Note.* ** $p < .001$, $N = 57$. Heatmap of motion tracking (**A.**). The lighter areas depict areas with more activity. B. Bar plots (**B.**) display time spent on the EPM areas during exploration trial (300 seconds = five minutes).

Furthermore, the evaluation of the first entry at the start of the exploration trial revealed that 59.6% of the participants entered the one of the open arms first.

Throughout the entire exploration phase, participants walked a mean distance of 709.52 (*SD* = 208.82) meters in total. Here, on open arms, the subjects walked 838.79 meters on average (*SD* = 38.12) whereas they walked 856.54 meters (*SD* = 334.82) on closed arms. T-test for paired samples was carried out to compare the means of walked distances between the two arm types, but found no significant difference ( $p = .719$).

#### *2.3.3.2 Exploration Behavior and associated traits*

To evaluate the relationship between psychometric traits and exploration behavior, Bonferroni-corrected correlation analyses ($p$ = .004) between time spent on the maze areas and the traits were conducted. Here, there was only a significant negative correlation was obtained between sensation seeking (SSS-V) and time spent in the center area, $r(55) = -.41$, $p = .002$. This finding indicates that sensation seekers are more prone to leave the center area for exploration. For all other correlations, no significant result was obtained ( $p > .129$).

Although no significant correlation was found between trait anxiety (STAI-Trait) and exploration behavior, an exploratory data analysis using the IQR (interquartile range) of the sum score of the STAI-Trait to create two extreme groups. Here, Q1 represented STAI-Trait sum scores ≤ 27 and Q3 was STAI-Trait sum score ≥ 45 with 15 individuals per group. In an attempt to determine whether there were differences in exploratory activity between the two extreme groups, mixed ANOVA with the between-group factors Q1 vs. Q3 and the within-group factor area (open vs. closed arms). No significant main ($p$ = .152) and interaction effect ($p$ = .500) was found which further supports the assumption that trait anxiety does not play a role in exploration behavior.

Correlation analyses with Bonferroni-corrected alpha level ($p$ = .003) were run to assess the relationships between psychometrics and walked distances on the various maze areas but no significant effects were found. For uncorrected p-value, only the negative correlation between walked distance in closed arms and claustrophobia (CLQ) was significant, $r(55) = -.29$, $p = .027$, indicating that high levels of claustrophobia are associated with less activity in the closed arms of the city EPM.

#### *2.3.3.3 Anxiety and arousal ratings*

Anxiety ratings were retrieved from all four arms but t-tests for paired samples for the ratings for closed and open arms found no differences (open arms: $p$ = .342, closed arms: $p$ = .588). Thus, in a second step the mean scores of open arms and closed arms ratings were computed and utilized for further testing. Finally, a t-test for paired samples (open vs. closed arms ratings) found a significant difference, $t(56) = -2.44$, $p = .018$, $d = -0.32$. In detail, participants experienced more anxiety on closed arms ($M$ = 7.57, $SD$ = 12.18) in comparison to open alleys ($M$ = 3.81, $SD$ = 8.97).

To estimate the relationship of psychometrics and anxiety ratings, Bonferroni-corrected correlation analyses ($p$ = .006) were computed, but no significant results were obtained. For

uncorrected values ($p < .05$) only a positive association was found between claustrophobia (CLQ) and anxiety rating on closed arms, $r(55) = .33$, $p = .013$.

Similar to the anxiety ratings, the four different arousal ratings were summarized and the means of the open or closed arm ratings were then used for statistical analyses. The comparison of the arousal ratings on open ($M = 28.36$, $SD = 22.04$) and closed arms (M = 36.61, SD = 22.64) using a t-test for dependent samples revealed no significant difference, $t(56) = -1.72$, $p = .091$, $d = 0.23$. In addition, no significant correlation with psychometrically assessed data was found ($p > .218$).

#### *2.3.3.4 Correlation of psychometric traits*

Correlation analyses of the total scores of the psychometric questionnaires to check for intercorrelations revealed a significant relationship between trait anxiety (STAI Trait) and anxiety sensitivity (ASI-3), $r(55) = .675$, $p < .001$. This corroborates earlier findings. Surprisingly, anxiety sensitivity (ASI-3) also positively correlated with sensation seeking (SSS-V), $r(55) = .32$, $p = .017$ and claustrophobia $r(55) = .35$, $p = .008$.

### 2.3.4 Discussion

This study aimed to investigate the influence of trait anxiety and personality traits on exploration behavior in a modified version of the prototypical EPM. A shift from the initial minimalistic design to a more human-like enriched version was conducted, and height situations were eliminated to inhibit interferences with acrophobic tendencies. Additionally, the virtual scenario was developed with another software (Unreal Engine 4) and presented in an HMD (HTC Vive Pro) to reinforce the economic advantage and enhance participants' immersion and presence. Furthermore, arousal ratings were introduced to gain further insight into subjective emotional experience during VR exposition. The experimental procedure was not changed for consistency and remained equivalent to the initial protocol.

Again, and equivalent to the findings of Study 2, no general preference for any maze area during the exploration trial was found. Although the center area of the maze was less frequented than open and closed arms, this result is likely due to the nature of the center area being a transition zone, i.e., this difference of spent time is instead an indicator of general activity per se. In line with the two previous studies, these results underscore that without apparent anxiogenic elements activating potential phobias there are no distinct exploration patterns in the human sample leading to area preferences.

Furthermore, open and closed arms activity could not be linked to the psychometric data. This is even more remarkable considering the preselection process and the extreme group comparison based on the STAI Trait score. However, the group comparison suffers from a reduced sample size resulting in a decrease in statistical power. Nevertheless, the results of the other analyses using the entire data sample emphasize that trait anxiety is not involved in EPM behavior.

Interestingly, a "preference" based on maze position was found in anxiety ratings. Subjects experienced more fear in closed than open maze alleys, suggesting claustrophobic potential. This finding also reflects the finding that higher anxiety ratings on closed arms are positively associated with claustrophobia assessed by the CLQ. Although one participant was found to have a critical claustrophobia score (CLQ Total Score > 51.8; Radomsky et al. (2001)), the effects remained stable after removal within the course of an exploratory reanalysis. Considering the results of the two previous studies, one possible explanation might be that in this version of the EPM, the perceived narrowness of the closed arms becomes the most salient "anxiogenic" factor. On the other hand, this bias is not reflected in the general ambulation patterns but only in the anxiety ratings and in association with the CLQ Score. Granted that these ratings are, again, remarkably low, the exact role of subclinical levels of claustrophobia remains inconclusive. Henceforth, one could assume that this is merely the result of discomfort rather than actual fear as claustrophobia levels in the sample were far from the clinical threshold.

In addition, a distinct trend regarding the arousal ratings was not observable as there was no association with maze areas or psychometrics. However, the arousal ratings were noticeably higher than the anxiety rating, indicating that subjects reacted to the virtual environment. Nonetheless, it remains disputable whether this effect originates from the feeling of novelty with the VR environment or equipment or is the result of the experimental manipulation per se. Nevertheless, it can be concluded that data collection of participants' arousal state might add as a valuable variable for future studies.

This study changed the navigation technique to virtual teleport instead of walking on foot or gamepad. As simulator sickness can be a limiting factor in VR research, this technique shift was on the one hand owed to limited lab room size in proportion to virtual maze size, which makes walking by foot only possible to a certain extent, and on the other hand to avoid motion sickness when "gliding" through VR scenario. On the downside, teleporting is not a natural part of human spatial locomotion in real life, consequently having the possibility to impair presence feeling when "jumping" through the scenario with one click on the controller.

It remains disputable how teleport affects presence and immersion feeling. Therefore, future experiments should also focus on the authenticity of locomotion options in VR, especially when working with large-dimensioned VR maps. In this, interfaces like the Virtualizer ELITE 2 (Cyberith GmbH, see https://www.cyberith.com/virtualizer-elite/ for further details), an apparatus resembling a round treadmill, provide the practicability of natural and physical walking through a virtual scenario while simultaneously requiring very little lab space.

Total exploration time also needs to be discussed regarding the dimensions of this virtual EPM version. According to the initial rodent experimental protocol, exploration time is set to five minutes (Belzung & Griebel, 2001; Bourin et al., 2007; Hogg, 1996; Pellow et al., 1985; Rodgers & Shepherd, 1993). For better comparison, this timeframe was maintained throughout all studies. However, in the current experiment, the dimensions of this city maze suggest that increase of exploration time might be preferable as it cannot be ruled out that due to unfamiliarity with the navigation system and VR equipment per se, although trained before, there is either a delay in exploration start or a general deceleration of movement. Furthermore, as exploration behavior is restricted to walking and visual inspection of details of the VR scenario (e. g., trees), some aspects of exploration behavior data likely lead to misinterpretation of results. For instance, an enduring inspection of, e.g., shop façades might have led to the increased time spent on a closed alley when analyzed over a timeframe of five minutes. Furthermore, closer inspection of subjects' data shows a large dispersion of covered distances during exploration trial ranging from 302 meters to 1294 meters is observed. As a result, the experimental procedure should either be changed from a time-bound to a distance-bound exploration trial, or differences in walked distances should be accounted for statistically.

In addition to maze dimensions, the general design of the city EPM states a challenging issue as well. As materials were predominantly retrieved from Showdown VR Demo (Epic Games, 2015), closed alleys resembled a typical American city, i.e., multi-storied brick row houses. Regarding unfamiliarity with this type of townscape, it is likely that these alleys were perceived as more captivating but also more threatening. Additionally, utilized props such as trash bags and garbage bins and dilapidated shop façades presumably challenge the feeling of security on those alleys, which is reflected in higher anxiety ratings but not exploration behavior channeled as a nonclinical form of claustrophobia. Therefore, for future experiments, it is advisable to design the city environment in conformity with the German cityscape while at the same time ensuring it is not a one-to-one copy of any major German city to avoid recognition bias. Moreover, it is highly advisable to conduct pilot studies to evaluate the valence of the

maze and alley design to ensure that preference of alley type does not trace back to either too positive or negative blueprint of maze arm, especially in the city context.

To enhance presence and maintain authenticity and realism of virtual scenario suitable background sound in dependence of position in the maze was incorporated. For the closed arms of the maze, an ambient city sound without human voices was chosen since no virtual agents were present. Nevertheless, ambient sound on closed arms comprised the sound of driving cars. As the navigation area was strictly limited to the road, excluding sidewalks, this could have led to increased discomfort on closed arms. However, two participants explicitly asked whether walking on the sidewalk was possible as they were worried about being overrun by cars. This indicates that ambient sound and virtual scenarios need to coherently match for future studies to inhibit distortions and confusion among participants.

In answer to the immensely low anxiety ratings in previous studies and thus to broaden validity of emotional states during exploration trial, in this study, data on participants' arousal were collected via rating. Although no differences depending on maze arm was found, arousal ratings were significantly higher than anxiety ratings. As previously discussed, this finding is not surprising as the Plus-Maze does not seem to be anxiogenic intrinsically. However, this also arouses whether anxiety ratings are a valid instrument in association with the human EPM, granted that the animal model proposes anxiety to be eligible for arm preference or avoidance. Similarly, increased anxiety ratings were solely found in a relationship with phobic fears, i.e., acrophobia in the precursory experiments but not trait anxiety or anxiety sensitivity. Although in the city EPM arousal ratings were uncorrelated with any character or anxiety trait, one possibility is to include psychophysiological measures such as heart rate or skin conductance measurement as outcome variables to cover for invisible and unconscious stress responses in reaction to EPM arms.

The present study showed that evolvement to a more naturalistic virtual environment is also a feasible alternative to the rather minimalist design of the "classic" EPM approach. This is overtly shown in the increased exploration behavior. This indicates that exploration behavior can easily be induced with appropriate design so that verbal instructions to start exploration can be minimized. Also, the tracking data results reversely emphasize the findings of the two earlier experiments. In the first and the second EPM study, tendencies in exploration behavior were only detectable in association with potential phobic stimuli, namely height of the entire platform (Study 1 and 2) or narrowness in association with closed arms (Study 1). For this city EPM, no preference was observed as no evident phobic elements were included in the scenario on purpose

# General discussion

This dissertation project was undertaken to design a virtual human model of the rodent EPM and evaluate cross-species validity in terms of general application and associated anxiety and personality traits. Primarily, the conducted studies were set out to investigate the exploratory activity, their changes regarding platform modifications, and their scientific implications in the context of translational research.

Coming from the findings of fundamental rodent research, the focus was set on the identification of general anxiety traits, i.e., trait anxiety, as the shaping variable of ambulatory activity on the virtual EPM. Specifically, it was hypothesized that humans like rodents display open arm avoidance, that this avoidance is linked to trait anxiety and is independent of specific phobias such as fear of heights (acrophobia), agoraphobia, and claustrophobia. If the cross-species validity was verifiable, the human virtual EPM would be the first behavioral test for trait anxiety and contribute to a greater understanding of subclinical risk factors and their progression to a fully developed mental disorder, highlighting this crucial topic from a preventive point of view.

## 3.1 Human exploration behavior on the virtual EPM

The data on exploration behavior collected over three studies suggest that human exploration behavior on the EPM does not follow the distinct patterns observed in rodents. Contrary to rodent studies, in Study 1, an open arm approach was observed, whereas for Study 2 and Study 3, ambulatory activity did not differ between the two arm types. Under those circumstances, the contradictory and inconclusive results hint at the lack of etiological conserved ambulatory preferences on this platform. Instead, it became evident that center (non)activity can serve as an indicator variable for general EPM activity. Granted that the center area of the maze serves as a transit zone, less activity here, time or distance based, indicates more activity on either the closed or open arms just like rodent center activity is used as an indicator of locomotor activity, a behavioral factor that is affected by sedative drug agents directly (File & Zangrossi, 1993; Rodgers & Johnson, 1995).

Nevertheless, one of the key problems is that the human EPM is a relatively new translational approach with only one published study in humans apart from the data presented here (Biedermann et al., 2017) but almost 11000 published studies with animals (Web of Science, 2021). Under those circumstances, one major drawback of this virtual human EPM is that data on spontaneous exploration behavior in humans is scarce, which limits the

comparability immensely, as so far, studies on human exploration behavior mainly utilized the Open Field paradigm and focused on abnormalities in the context of mental health issues, e.g., bipolar disorder and schizophrenia (Perry et al., 2009). For instance, both Walz et al. (2016) and Gromer et al. (2021) detected human thigmotaxis. However, Walz and colleagues (2016) demonstrated that human thigmotaxis is associated with anxiety sensitivity and agoraphobia, whereas Gromer and colleagues (2021) were unable to observe any associations with anxiety traits. Therefore, it seems crucial to retrieve data on natural exploration behavior tested in VR, real life, or the environment to be tested. This might be implemented by conducting pilot studies with a large sample size to acquire an unbiased insight into general movement patterns and, therefore, identify deviant behavior when testing specific populations or VR scenarios.

Based on this need for baseline exploration data, the behavioral indices concerning the anxiogenic nature of the EPM have to be discussed critically. In rodents, the apparatus triggers the instinctive fear of being killed by a predator, and the displayed EPM behavior (avoidance) is congruent with the one described in the Predator Imminence Theory (Fanselow & Lester, 1988; Perusini & Fanselow, 2015). Hence, open arm avoidance and closed arm approach function as a protective behavioral pattern to seek shelter from (aerial) predators (Barnett, 2017). Presumably, in applying the EPM to humans, there are limits to how far the concept of the Predator Imminence Theory can be taken as humans do not have aerial predators. However, given that cross-species validity of the EPM might be present, the translational approach, on the one hand, implies that in the virtual EPM, humans also experience a potentially life-threatening situation. On the other hand, the findings of Gromer et al. (2021) showed that these behaviors seem to be evolutionary conserved and are displayed without an actual threat or a psychometric disposition. However, critics of these spatiotemporal measurements contend that such studies do not cover exploration behavior as a whole and point out blind spots that might be essential for behavioral anxiety research. For instance, in rodent research, Ohl (2003) and Rodgers, Cao, et al. (1997) advocated for the observation of risk assessment behaviors and suggest finer-grained analyses in general as a supplement to the “classic” measures. For human exploration, the research suggests information-seeking behaviors such as visual exploration (Einhäuser et al., 2007) or object interaction (Perry et al., 2009). Specifically, on the human EPM, this might emerge as the attempt to touch parts of the virtual scenario (walls, handrails, grass), a general detailed inspection of the virtual environment, or even trying to test the physical properties in VR presumably to test the security of the platform, e.g., trying to grab the handrail. These behaviors have all been observed occasionally but were not introduced to the data analyses as they were anecdotal and only showed up sporadically. One significant

advantage of synthesizing these different aspects would be that the future research community could rely on exploratory pattern profiles that can be used universally across the different research approaches and utilize them as a baseline if testing for deviations.

Unlike rodent research, these three studies introduced walked distance as an indicator of general activity and complemented the spatiotemporal data, although it did not provide further meaningful insights. However, walked distance could help identify human freezing behavior (Roelofs, 2017) as there would be a discrepancy in time spent in one area and walked distance.

### 3.2 Exploration behavior and anxiety

One of the central hypotheses in this dissertation project was how trait anxiety shapes human exploration behavior on the virtual EPM. Specifically, it was assumed that trait anxiety independent of specific phobias is linked to open arm avoidance. However, the data suggest that trait anxiety does not play a significant role in open arm avoidance or shapes ambulatory tendencies at all. Instead, the main finding is that fear of height and claustrophobia significantly impact exploration behavior on the virtual human EPM. This challenges the cross-species validity of the apparatus and points out the incapability of the human EPM to measure trait anxiety.

Regarding the absence of consistent significant results of trait anxiety in association with exploration behavior, one has to discuss the anxiogenic nature of the virtual human EPM per se. As described earlier, trait anxiety is defined as an individual's disposition to react with (transitory) state anxiety and to perceive ambiguous situations as threatening much faster than someone with less trait anxiety (Wiedemann, 2001). Furthermore, as discussed in the discussion of Study 2 (see section 2.2.4), humans are imprinted by their evolutionary conserved anxiety history (preparedness theory of Seligman (1971)). While this would explain open arm avoidance and anxiety based on acrophobia (Biedermann et al., 2017), as falling off a (virtual) cliff is indeed a fatal incident, it might also offer an explanation on why the anxiety ratings throughout all studies were low and why small, or no effects were found for trait anxiety or anxiety sensitivity. This suggestion becomes remarkably apparent in Study 3, in which no height situation is present in VR, and the focus of anxiety ratings, but not behavioral avoidance instead shifts to the closed arms of the EPM and becomes linked to claustrophobia - another "prepared" phobia (Mineka & Öhman, 2002). The observed association of acrophobia and open arm avoidance also replicates the findings of Biedermann et al. (2017). Nevertheless, their paper claims that cross-species validity is present as both humans and rodents avoid open arms

naturally (Biedermann et al., 2017). Although innovative, the mixed reality design is limited by the fact that the utilization of the wooden cross (20 cm height) used for haptic feedback for the virtual EPM probably accounts for triggering fear of height. Taken together with the height of the virtual EPM (55 meters) and provided that Treit et al. (1993) found that maze height is not an anxiogenic variable that influences rodent EPM behavior, it is assumed that rodent EPM activity reflects general anxiety and Biedermann's (2017) study is in fact not a validation of the human EPM but more so a test for acrophobia (Bach, 2021).

The data revealed that anxiety sensitivity does not play any pivotal role in EPM behavior or subjective experience reflected in the anxiety or arousal ratings. At the same time, anxiety sensitivity shares a significant amount of variance with trait anxiety. This also replicates findings of other research groups (McWilliams & Cox, 2001; Plehn & Peterson, 2002) who found highly positive and significant correlations between the two concepts putting the distinctiveness of the two concepts into question at first glance. However, one has to keep in mind that clinically anxiety sensitivity is associated with panic disorders (Muris et al., 2001; Plehn & Peterson, 2002; Taylor et al., 1991), a factor that naturally is not entirely reflected in exploratory activity on the human (or rodent) EPM while trait anxiety leans more towards generalized anxiety disorders and depression (Kennedy et al., 2001; Knowles & Olatunji, 2020). Consequently, it is not entirely surprising that an effect for trait anxiety was observed in the first study but not for anxiety sensitivity.

In summary, it can be assumed that the nonclinical, but elevated levels of phobic fears overpowered trait anxiety, which is reflected in either exploration behavior or anxiety ratings. Also, this might hint at the possibility that general anxiety does not necessarily derive from an evolution-based process. Consequently, these studies provided valuable insights on the hierarchy of the different anxiety domains, although some authors suggest a genetic base for trait anxiety, specifically in association with the serotonin transporters (Schinka et al., 2004; Straube et al., 2014). At the same time, the concept of trait anxiety, along with the STAI, attracted a considerable amount of criticism as studies showed that it more so reflects negative affect and is conceptually closer to depression than anxiety (Bados et al., 2010; Balsamo et al., 2013; Knowles & Olatunji, 2020). For this reason, current research turns to concepts such as Intolerance of Uncertainty (IU; Carleton, 2016a; Carleton et al., 2012; McEvoy et al., 2019) and Fear of the Unknown (FOTU; Carleton, 2016b) which better envelop higher cognitive functions of human anxiety and reflect the dimensional nature of general anxiety better. However, IU, just like trait anxiety, is not exclusively part of the anxiety disorder spectrum but also covers the worry component of depression and other disorders (Dar et al., 2017). Under

those circumstances, it remains inconclusive whether a virtual human EPM can selectively provide insights into general human anxiety to cross-validate it or whether it serves as a more general tool in identifying underlying behavioral patterns of various mental disorders on a preclinical stage. However, regarding the latter, this would aggravate the discriminatory power of the apparatus and push the categorical boundaries of the current diagnostically systems of both the DSM-V (American Psychiatric Association, 2013) and the ICD-11 (World Health Organization, 2019). On the other hand, this could expand the current knowledge on the etiology of anxiety disorders and sufficiently add to the translational process.

Nevertheless, if sticking to the objective of utilizing the human EPM to examine ambulatory patterns linked to general anxiety, whether IU, FOTU, or trait anxiety, future research is required to use specific methods to avoid phobia-activated fear. For instance, the threat of shock paradigm induces anxiety by informing participants that at some point throughout the experimental procedure, they will receive one or several aversive electrical stimuli (Robinson et al., 2013). As a result, this induces a state in which the individual feels constantly threatened, and several studies showed that the threat of shock paradigm is a valuable method to trigger trait anxiety-associated processes (Clark et al., 2012). For instance, in order to avoid adverse outcomes, i.e., harm avoidance, trait anxious persons (Charpentier et al., 2017; Sussman et al., 2016) tend to make disadvantageous decisions (Bublatzky et al., 2017) or display an attention bias towards threat stimuli (Edwards et al., 2010; Okon-Singer, 2018; Robinson et al., 2013) in comparison to non-trait-anxious subjects. Alternatively, affective priming is also an acknowledged tool to provoke anxiety (Lee et al., 2011; Neumann & Lozo, 2012; Yang et al., 2016). Therefore, these two methods could aid in stimulating trait anxiety-related state anxiety on the virtual human EPM and thus enable an emotional state similar to one of the rodents when on the EPM. In line with combining various methods, one can extend the behavioral outcome measures as mentioned before. For general anxiety, this could cover behaviors such as distance to platform edge (see Gromer et al., 2018 for an example) or other behavioral indices, such as hesitation in entering platform arms or repeated inquiries on whether the participant is doing “everything right”. Especially the latter hints at the subjects’ need to gather information on the ambiguous threat to feel safer. This would refer to the first stage of the Predator Imminence Theory, in which the level of (non)dangerousness of a situation still needs to be examined (Perusini & Fanselow, 2015). However, at the same time, these risk-assessment behaviors must be differentiated from the feeling of novelty and insecurity with the VR environment or equipment. Nevertheless, this could be controlled by increasing the training time or evaluating participants’ previous VR or gaming experience.

In the light of the collected data on psychometrics, the influence of sensation seeking on ambulatory activity was somewhat surprising. Traditionally, sensation seeking is associated with risky behavior and an increased tendency to approach novel situations (Neary & Zuckerman, 1976; Roberti, 2004; Zuckerman, 2007). Regarding EPM activity, it was found that sensation seekers tend to experience less anxiety on the maze, express open arm approach, and closed arms or center area avoidance. Furthermore, sensation seeking is often diametrical to psychometric data on phobia-related data assuming that individuals with high levels of sensation seeking tend to express less acro- or claustrophobia and vice versa. While EPM behavior is still best explained by individuals' level of fear of height, the extent of the relevance of sensation seeking is still remarkable and does not replicate the results of Biedermann et al. (2017), who connected sensation seeking with open arm approach. However, a closer inspection of the SSS-V (Beauducel et al., 2003) revealed that multiple items of this questionnaire share significant conceptual overlap with the AQ (Cohen, 1977) as they describe to some extent extreme height-associated situations, e.g., "I would like to try parachute jumping" vs. "I would never want to try jumping out of a plane – with or without a parachute" (Beauducel et al., 2003). Therefore, it cannot be ruled out that sensation seeking and associated exploratory activity is entirely independent of acrophobia, although the questionnaire intercorrelations assume that there is either no or a minor relationship present. Nevertheless, future studies need to consider this data confounding, especially with high acrophobic individuals or high sensation seekers.

## 3.3 Limitations

The three experiments were set out to explain human exploration behavior on the virtual EPM and examine associated traits. However, several limitations need to be discussed.

Usually, research on emotion includes a variety of measures. This includes but is not limited to physiological variables such as skin conductance, startle reflex, or heart rate variability (Lang, 1985; Lang et al., 2000). However, the current experiments are limited by the absence of these essential data, as they could have complemented the subjective (ratings) and explorative variables. For example, fear habituation over the five minutes of exploration cannot be entirely excluded regarding the low anxiety ratings. Therefore, collecting physiological data would have been beneficial to monitor these indices over the time course of the exploration trial.

In addition, one of the limitations of all three studies stems from the sample selection process. Firstly, due to a lack of resources, student convenience sample were tested in all three studies. Therefore, this significantly impairs generalization across the general population.

Secondly, trait anxiety levels did not exhibit the variability necessary to test for notable group differences. In all three studies, the means STAI trait sum scores ranged from approximately 34 to 37, representing average levels of trait anxiety which is a bit disappointing regarding the fact that subjects were screened for this trait as usually pathological high trait anxiety scores start at 55 (Charpentier et al., 2017). Naturally, this might restrict reliable statements on the influence of trait anxiety on exploration behavior, although the sum score ranges were quite broad. Under those circumstances, it might be advisable to screen for extreme groups for better comparison. However, studies found that high levels of trait anxiety are also associated with an increase in anxiety disorders (Ercan et al., 2015). The screening data also suggest that high trait anxious individuals often exhibit elevated screening scores for the other anxiety disorders. Considering the research objective, i.e., detecting the influence of trait anxiety independent of anxiety-related psychopathological conditions, this represents a challenging issue and hints at the samples' particularity used in the three experiments. Under those circumstances, it seems necessary to shift the research focus to other domains that better reflect an individual's anxiety disposition even though trait anxiety as measured by the STAI (Laux et al., 1981) looks back on decades of research history.

Another point of criticism refers to spatial perception in VR, which states an ongoing issue since the beginning (e. g. Arthur et al., 1997; Interrante et al., 2008; Paes et al., 2017; Wann et al., 1995). For instance, Armbrüster et al. (2008) and Peillard et al. (2019) found that visual depth perception is often distorted in VR, i.e., virtual distances are often estimated inaccurately. Furthermore, the authors found that stereopsis, i.e., the ability for three-dimensional vision, associated with binocular ability, plays a crucial role in distance perception (Armbrüster et al., 2008). At the same time, amblyopia, an ophthalmologic condition associated with disturbances in binocular ability in adults (often as a result of untreated strabismus during childhood), has a prevalence of five to eight percent in the general population and is even higher in those wearing glasses (Rüping & Kook, 2011). Consequently, ophthalmologic impairments leading to distorted distance perception could influence exploratory activity in any virtual scenario and should be considered in the sample selection process. Regarding the virtual scenarios used in the thesis this could have been displayed in perceiving the closed arms as narrower as they were designed. As a result, this could explain the tendency to avoid arms with high walls or high houses.

Finally, participants occasionally mentioned that the virtual scenario gives a somewhat artificial impression, and this concern was mainly expressed in the first two studies in which the EPM design was closest to the rodent EPM. While one can debate that this is necessarily a

part of the cross-species translational process, it also represents a critical limitation as it automatically assumes that the simplicity of the apparatus design is also suitable for humans. In return, this might have influenced exploratory activity while at the same time pointing towards the fact that virtual scenarios need a certain amount of sensory enrichment. With this intention in mind, future researchers find themselves caught between creating an EPM that is in line with a realistic human touch while avoiding environmental cues that cause either avoidance or approach and thus distort human ambulation.

## 3.4 Summary and outlook

Transferring established animal models to humans to validate them translationally and to stimulate the research framework to provide more insights and improve mental health care has gained momentum over the last decade (Grillon et al., 2019). In the long run, these translational projects are set out to transcend research boundaries and fill the scientific gap that restrains the development of novel therapeutic approaches, especially in anxiety disorders.

This dissertation project was undertaken to design an elevated human plus-maze and evaluate the cross-species validity of this apparatus utilized for decades in rodent anxiety research. Here, the main goal was to 1) detect correspondent evolutionary conserved exploration tendencies, i.e., open arm avoidance, 2) connect the data on EPM ambulation to general anxiety traits that are viewed as risk factors in the development of anxiety disorders in humans and finally 3) add to the translational research framework to stimulate the scientific progress. Throughout three studies, this thesis identified no indications of the hypothesized cross-species validity. In fact, the results imply that humans do not have a distinct exploration pattern reflected in either avoidance or approach of certain EPM areas and that avoidant ambulatory activity is driven predominantly by subclinical phobia-derived fear about height or narrowness. Remarkably, these avoidance tendencies are only detectable if associated with the psychometric data and not on a broad-spectrum. Coupled with the growing literature on subthreshold anxiety disorders and their impact (Bosman et al., 2019; Carter et al., 2001; Haller et al., 2014; Karsten et al., 2011; Lewinsohn et al., 2004; Okasha, 2009), these findings along with others might add to the etiological explanatory models and challenge the current categorical approach utilized in the diagnostical process. Granted that only healthy subjects and no patient groups were examined in all studies, the results entail the notion that, on the one hand, conspicuous features of anxiety disorders are present long before an actual disorder onset. Also, the indications drawn from the results presented above contrast those of Biedermann et al. (2017) as they presume the existence of a perfect translation of the EPM from rodents to humans while simultaneously

disregarding the significance of fear of height on humans but not rodent EPM activity (Martínez et al., 2002; Treit et al., 1993). Consequently, for future translational research in humans and animals, there is an urgent need to more clearly separate fear and anxiety, as emphasized by Robinson et al. (2019). Nevertheless, the studies of this thesis and the studies taken out by Biedermann et al. (2017) provided valuable insights and showed that virtual reality is a suitable, economic, and efficient tool for translational research. Consequently, VR will likely continue to play an important role in psychological research.

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# Appendix

**Appendix A.** Hierarchical regression analyses on EPM behavior and psychometric data of Study 2 after exclusion of one participant with AQ-Acro sum score = 62

| | ***R2*** | ***AIC*** | ***B*** | ***SEB*** | ***β*** | ***p*** |
|---|---|---|---|---|---|---|
| *Step 1* | .04 | 603.15 | | | | .029 |
| Intercept | | | 94.69 | 18.50 | | <.001** |
| STAI Trait | | | .85 | .48 | .23 | .080 |
| *Step 2* | .09 | 600.89 | | | | .007* |
| Intercept | | | 108.22 | 19.19 | | <.001** |
| STAI Trait | | | .83 | .46 | .22 | .070 |
| AQ Anxiety | | | -.85 | .41 | -.26 | .045* |
| *Step 3* | .07 | 598.71 | | | | .002* |
| Intercept | | | 108.30 | 31.41 | | .001* |
| STAI Trait | | | .86 | .48 | .23 | .078 |
| AQ Anxiety | | | -.85 | .44 | -.26 | .061 |
| SSS-V | | | -.003 | .90 | < .001 | .998 |
| *Step 4* | .05 | 600.68 | | | | .006* |
| Intercept | | | 108.24 | 32.70 | | .002* |
| STAI Trait | | | .86 | .48 | .23 | .081 |
| AQ Anxiety | | | -.85 | .49 | -.26 | .088 |
| SSS-V | | | -.002 | .92 | -.002 | .999 |
| CLQ | | | -.003 | .44 | .001 | .995 |

*Note. *p < .05, **p < .001. $R^2$ = adjusted $R^2$. STAI = State-Trait Anxiety Inventory, ASI-3 = Anxiety Sensitivity Index, AQ = Acrophobia Questionnaire, SSS-V = Sensation Seeking Scale, CLQ = Claustrophobia Questionnaire. N = 60.*

# Publication List

## Research Articles in Peer-Reviewed Journals

**Madeira, O**., Gromer, D., Latoschik, M. E., & Pauli, P. (2021). Effects of Acrophobic Fear and Trait Anxiety on Human Behavior in a Virtual Elevated Plus-Maze. Frontiers in Virtual Reality, 2, 19. doi: 10.3389/frvir.2021.635048

Gromer, D., **Madeira, O.**, Gast, P., Nehfischer, M., Jost, M., Müller, M., Mühlberger, A. & Pauli, P. (2018). Height simulation in a virtual reality CAVE system: validity of fear responses and effects of an immersion manipulation. *Frontiers in Human Neuroscience*, 372.

# Curriculum Vitae

# Affidavit

I hereby confirm that my thesis entitled “The Human-Experimental Virtual Elevated Plus-Maze as an Anxiety Model” is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/or materials are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

…….  ….……

Place, Date  Signature

# Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation „Das human-experimentelle virtuelle Elevated Plus-Maze als Angstmodell“ eigenständig, d.h. insbesondere selbstständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegeben Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

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