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Fear behavior in virtual reality

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Table of content

List of abbreviations

CS	conditioned stimulus
CS-	conditioned safety stimulus
CS+	conditioned threat stimulus
HMD	head mounted display
iVR	immersive virtual reality
US	unconditioned stimulus
VR	virtual reality

List of publications

Binder, F. P., and Spoormaker, V. I. (2020). Quantifying Human Avoidance Behavior in Immersive Virtual Reality. *Front. Behav. Neurosci.* 14. doi:10.3389/fnbeh.2020.569899.

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Pöhlchen, D., Leuchs, L., **Binder, F. P.**, Blaskovich, B., Nantawisarakul, T., Topalidis, P., et al. (2020). No robust differences in fear conditioning between patients with fear-related disorders and healthy controls. *Behav. Res. Ther.* 129. doi:10.1016/j.brat.2020.103610.

Pöhlchen, D., Priouret, M., Kraft, M. S., **Binder, F. P.**, Gürsel, D. A., Berberich5, G., et al. (2021). Examining Differences in Fear Learning in Patients With Obsessive-Compulsive Disorder With Pupillometry, Startle Electromyography and Skin Conductance Responses. *Front. Psychiatry* 12. doi:10.3389/fpsyt.2021.730742.

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Heinz, D. E., Schöttle, V. A., Nemcova, P., **Binder, F. P.**, Ebert, T., Domschke, K., et al. (2021). Exploratory drive, fear, and anxiety are dissociable and independent components in foraging mice. *Transl. Psychiatry* 11. doi:10.1038/s41398-021-01458-9.

My contribution to the publications

Contribution to paper I

The work of paper I (Binder & Spoormaker, 2020) was done by me under supervision of Victor Spoormaker (VS). In detail:

I built the virtual reality laboratory, including selecting and ordering the equipment and developing the software to run it, as well as developing the virtual environment in Unity3D. Together with VS, I designed the study and wrote the ethical proposal under his supervision. I developed and implemented the tasks, recruited the participants, and acquired and analyzed the data. Together we interpreted the data, and I wrote the manuscript under his supervision.

Contribution to paper II

The work of paper II (Binder et al., 2022) was done by me under supervision of Victor Spoormaker (VS) and support of Prof. Peter Zwanzger (PZ) and Dorothee Pöhlchen (DP). In detail:

Together with VS, I designed the study with support of PZ and DP. I developed and implemented the tasks, recruited the participants, acquired, and analyzed the data. Together with VS, I interpreted the data, and I wrote the paper under supervision of VS and contribution of PZ and DP.

1. Introductory summary

1.1 Fear and anxiety

Fear is an unpleasant emotional state eliciting defensive behaviors and serves to protect the organism (Kevin S. LaBar, 2016; Mobbs, 2018). A closely related emotional phenomena is anxiety. In contrast to fear, anxiety is defined as a state of unease about an anticipated, potentially negative outcome that is more distal and future-oriented, whereas fear is defined as a response to an impending threat and typically has an identifiable triggering stimulus (American Psychiatric Associaton, 2013; Kevin S. LaBar, 2016; Öhman, 2008). Fear and anxiety enable us to escape from and avoid dangerous and threatening situations, and thus serve to survive. However, if they are exaggerated and cannot be appropriately regulated they might lead to an anxiety disorder (Quinn & Fanselow, 2006). With a 12-month prevalence of 14%, anxiety disorders are the most frequent mental disorders (Wittchen et al., 2011). They share features of recurrent excessive anxiety, behavioral disturbances - typically avoidance behavior, and distress or impairment in important areas of functioning. The anxiety disorders are classified by the feared situations and the content of the associated beliefs and thoughts (American Psychiatric Association, 2013). For instance, specific phobia is characterized by intense fear of a specific object, animal, or situation, such as a spider in arachnophobia, which is the most common specific phobia.

Fear and anxiety research aim to understand the causes of anxiety disorders and to develop new treatments. But how can fear be studied? According to Lang, fear is manifest in three dimensions: On the subjective dimension, participants are asked how fearful they feel or how uncomfortable they feel about an object or animal. On the physiological dimension, fear can presumably be observed in heart rate, skin conductance, eye-blink startle, respiration, pupil size, and more. Finally, fear manifests itself in behavior, such as avoidance behavior. While human research mainly uses the subjective and physiological dimensions, animal research primarily relies on the behavioral dimension (Lonsdorf et al., 2017). This discrepancy complicates and questions the translation of knowledge from one species to another. Especially since the relationships between the dimensions are complex rather than simplistic. One way to address this gap is to use new technologies to advance the study of human fear behavior.

To study the causal structure of fear, an experimental manipulation is necessary. A well-established paradigm to do this is Pavlovian fear conditioning (Lonsdorf et al., 2017). In this procedure, a typically former neutral stimulus is presented together with an unpleasant stimulus (US) and thus becomes the conditioned stimulus (CS). The type of neutral and unpleasant stimuli can be diverse. For example, a geometrical figure presented on a monitor could be used as CS and followed by a mild electrical shock as US. But the CS could also be a sound, or any other perceivable stimulus. In differential fear conditioning, another neutral stimulus is added and presented without pairing with the US, thus becoming the safety stimulus (CS-). In this procedure, the threatening CS, which is paired with the US, is usually referred to as CS+ to distinguish it from the CS-. In some studies, this conditioning phase is followed by an additional extinction phase in which the CS+ is presented without US, thus extinguishing the fear response to the CS+.

In a large-scale study of a group colleague (Pöhlchen et al., 2020), a differential fear conditioning paradigm was used to investigate differences between a group of patients with anxiety disorders and a group of healthy controls. In this setup, geometric figures presented on a monitor in front of participants were used as CS and mild electric shocks at the right wrist or air blasts to the larynx were used as US. The subjective dimension was assessed by asking about the expectation that one of the US followed the CSs. On the physiological dimension, pupil diameter, skin conductance, and startle electromyography were measured. Despite this variety in measurements, no robust group differences between patients and healthy controls were detected. Neither during conditioning nor during the additional phases afterwards and on the next day. Moreover, this finding has been backed up by more recent, large-scale studies (Abend et al., 2020; Duits et al., 2021; Savage et al., 2020). This challenges the assumption that generic conditionability contributes to the development of anxiety disorders. Moreover, it challenges the view that physiological readouts are relevant as a potentially clinical readout for anxiety disorders, even though this is implicit in multiple emotion theories. At the same time, no physiological biomarker exists for diagnosing any of the anxiety disorders. The question therefore seems to be if there are any objective readouts that are closer to the subjective phenomenology than physiology, such as behavior and in a context of fear, avoidance behavior.

1.2 Avoidance behavior

Avoidance behavior limits normal functioning and is a key symptom of anxiety disorders (American Psychiatric Association, 2013). Furthermore, it maintains fear by preventing extinction (P. F. Lovibond et al., 2009): a person who always avoids a feared object or animal, cannot learn that it is not dangerous. Therefore, overcoming avoidance behavior is also a central goal of anxiety disorder treatment (Bandelow et al., 2021) and is trained in exposure therapy (Foa & Kozak, 1986). Avoidance behavior is usually assessed on the subjective dimension by self-report with questionnaires such as the Brief Experiential Avoidance Questionnaire (Gámez et al., 2014) or the Acceptance and Action Questionnaire (Bond et al., 2011; Hayes et al., 2004), or by observing the behavior in the behavioral approach test (Grös & Antony, 2006), in which individuals are confronted with the feared object and are asked to try to approach it as far as possible. In research, avoidance behavior is usually assessed in laboratories by pressing buttons or moving joysticks. This has provided valuable insights, for example, into the effect of cost of avoidance (Rattel et al., 2017), sex differences (Sheynin et al., 2014), or the mechanisms of avoidance learning (Pittig et al., 2020).

The mechanisms for the development of avoidance behavior have been intensely debated over the past century, and many theories of avoidance learning have been proposed (Krypotos et al., 2015). The most controversial point is the role of instrumental conditioning. Instrumental conditioning is a method of behavioral learning based on the consequences of the behavior (Skinner, 1948). The consequences can be punishment or reward, or the absence of one of these options if expected by the subject. One of the first avoidance learning theories was the two-factor theory of Mowrer (1951). According to this model, first Pavlovian fear conditioning is necessary to make a former neutral stimulus aversive. In a second step, instrumental conditioning is necessary to establish avoidance behavior through reinforcement by fear reduction. A major criticism of this theory is the following paradox: Avoidance behavior results in the omission of the US and thus a CS+ presentation occurs without the US, which should result in fear extinction. However, according to the two-factor theory, fear extinction eliminates the reinforcer of the avoidance behavior and thus the avoidance behavior itself should disappear. This paradox together with other phenomena that could not be explained by the two-factor theory yielded to the proposition of new theories, such as the Species-specific Defense Reactions (Bolles, 1970) and the safety signals theory. While these theories are mainly based on animal research and thus ignore cognitions, later human research yielded to the proposition of new theories considering expectations and propositions (De Houwer et al., 2005; P. Lovibond, 2006; Seligman & Johnston, 1973). Contemporary theories aggregate these theories (Krypotos et al., 2015) or extend them by habituation (LeDoux et al., 2017) as a solution for the former mentioned extinction paradox. Despite this long debate, the role of instrumental conditioning in avoidance learning is still unclear, and the question of its reinforcement is still open. New technologies may help to provide further data for this debate, including behavior tracking and virtual contexts.

Virtual reality (VR) is an environment that is generated by a computer and presented to the user. The form of the presentations varies from normal computer monitors to large, curved monitors up to VR caves with lightweight polarized goggles and head mounted displays (HMD). Modern HMDs usually include a motion tracking system based on accelerometers, laser distance measurements, or visual systems to track the position and rotation of the HMD and translate it to movements in the virtual environment. Both, the VR cave and the HMD, can present individual images for each eye and thus present a three-dimensional perspective. An important criterion to evaluate these presentation forms is immersion. Immersion describes the perception of being included, enveloped, and interacting with the technology that provides a continuous stream of stimuli (Witmer et al., 2005). While immersion is low in virtual realities presented on a monitor, it is higher in VR caves and HMDs. That is the reason why these technologies are referred to as immersive virtual reality (iVR). Compared to the VR caves, HMDs, such as the HTC Vive Pro, have the advantage of being much more cost-efficient, less space consuming, and easier to install. In psychological research iVR brings the advantages of providing full control over the environment, yielding the same setup for all participants and thus a high standardization. Simultaneously, all parameters and motions in the VR can be recorded for later analyses.

Kroes, Dunsmoor, Mackey, McClay, and Phelps (2017) used iVR to investigate the role of context on fear learning. They developed a differential fear conditioning paradigm with colored contexts as CS+ and CS- and electrical shocks to the right wrist as US. In their setup, participants were sitting on a chair wearing the HMD and were passively guided on a predefined path through the colored rooms. They observed CS+ and CS- differences in subjective valence and arousal ratings, in eye-blink startle responses, in skin conductance, and in retrospective shock estimations. The acquisition of subjective threat and the observation of fear-conditioned defensive responses showed that iVR can be used to perform fear conditioning paradigms.

In the first paper of my thesis (Binder & Spoormaker, 2020), we used iVR to investigate avoidance behavior after fear conditioning. We wanted to find out how participants behave towards fear conditioned stimuli, and if Pavlovian fear conditioning is sufficient to induce avoidance behavior or if additional instrumental conditioning is necessary. In our setup, participants wore an HMD, in-ear headphones, a full-body motion tracking system, and an electrocardiography device to measure the heart rate. After the introduction and the attachment of the electrocardiography electrodes as well as the motion tracking sensors, the VR started. The participants began in a tutorial scenario to habituate to VR and to train the interaction. Subsequently, they were placed into another scene for the fear conditioning task, with differently colored balloons as CS+ and CS- and mild electrical shocks on the left calf as US. The fear conditioning task was followed by our three behavioral tasks. To cover a broader range of avoidance behavior, we developed a behavioral search, a behavior forced-choice, and a behavioral approach task. The behavioral tasks differed in the degree of freedom, the task-relevance of the conditioned stimuli, and the gamification level.

The behavior within one task was naturally affected by the experience in all preceding tasks. Therefore, avoidance behavior was a single consequence of Pavlovian conditioning only in the first task that immediately followed the fear conditioning task. In the second and third behavioral task, participants' behavior was also a consequence of the experiences in the first and second task, respectively. In that way, the first two behavioral tasks functioned not only as readouts, but also as further learning tasks for the succeeding tasks. In each task, the CS+ was presented and its approach could either trigger an US or not, resulting in an additional reinforcement or non-reinforcement, respectively. This manipulation allowed us to investigate the effect of additional reinforcement and non-reinforcement on avoidance behavior in successive behavioral tasks. We hypothesized that Pavlovian conditioning is sufficient to elicit avoidance behavior and that additional reinforcement and non-reinforcement strengthen and extinguish this avoidance behavior, respectively.

We initially tested these hypotheses and examined the sensitivity of the procedure to assess avoidance behavior with four consecutive runs. Between the runs we modified the order of the tasks and the additional reinforcement during the behavioral tasks and fine-tuned the tasks. These runs were analyzed together as a quasi-experiment with 55 participants in total. We observed avoidance behavior in all behavioral tasks after additional reinforcement. However, when the task was performed without prior additional reinforcement, immediately after fear conditioning, avoidance behavior was detectable only in the behavioral forced-choice and the behavioral search tasks. Despite these promising results, attribution to Pavlovian fear conditioning and additional reinforcement was limited because there were some confounding influences: We changed the order and the occurrence of reinforcement between runs without randomization. Furthermore, we repeatedly made small optimizations between runs, such as rearranging the positions of the CSs. To examine the robustness of the findings, we performed an additional confirmatory experiment with 72 participants in which we systematically manipulated the order of the behavioral tasks and the reinforcement during them. Additionally, we increased the intensity of the US by using a 2 s female scream combined with three consecutive mild electrical shocks, as in the quasi-experiment, we observed more avoidance behavior the more the participants disliked the US. The effects were largely replicated in the confirmatory experiment: In the behavioral approach task, we detected avoidance behavior only after additional reinforcement whereas in the behavioral search task, we observed avoidance behavior already after the fear conditioning task. However, in the behavioral forced-choice task, avoidance behavior was only present after additional reinforcement, but not after Pavlovian fear conditioning as in the quasi-experiment.

These results are interesting in two respects:

In considering the process of avoidance learning, our results contribute to the long debate about the emergence of avoidance behavior and the role of instrumental conditioning: We observed that Pavlovian fear conditioning can be sufficient for avoidance behavior, as captured with the behavioral search task. However, this avoidance behavior was weak, as it was not present in all tasks. Further instrumental reinforcement enhanced the avoidance behavior to the level that it could be observed in all tasks. In addition, non-reinforcement in the behavioral tasks resulted in extinction of avoidance behavior in all subsequent behavioral tasks.

In considering the properties of the tasks, we were able to investigate the sensitivity to detect avoidance behavior and the consistency between tasks. The most sensitive task was the behavioral search task, with high degrees of freedom, low task-relevance of the CSs, and a high gamification level. The behavioral approach task, with low degrees of freedom, high task-relevance of the CSs, and a low gamification level, was the least sensitive one. The forced-choice task, with medium degrees of freedom, medium task-relevance of the CSs, and low gamification, was in between the other two and resulted in a bimodal distribution with participants having mainly strong or no avoidance behavior. Although the CS-US contingency was manipulated during the behavioral tasks, we found correlations between them. Furthermore, we found an effect of participant on avoidance behavior meaning they showed consistent avoidance behavior over all tasks. These individual differences could be explained by the influence of individually rated US valence in the experiment and individually rated CS+ valence in the quasi-experiment.

The individual differences and the correlation with stimulus valence raised the question how participants would behave if fear levels were even more increased. Especially, as no avoidance behavior of Pavlovian conditioned fear was detectable in the behavioral approach task. Only the increase of the fear level by additional instrumental reinforcement led to detectable avoidance behavior. For ethical reasons, we could not increase the intensity of fear resulting from the fear conditioning task. Therefore, as a next step, we focused on anxiety disorders in which the intensity of fear is, by definition, so high that it causes personal suffering. Focusing on anxiety disorders also has the advantage of moving one step closer to improving treatment and diagnosis, which is beneficial for patients. As our behavioral tasks were designed to investigate human behavior towards a specific object, we chose to investigate fear behavior in specific phobia in the next study.

1.3 Fear behavior in specific phobia

We have shown that fear after Pavlovian fear conditioning and additional reinforcement manifests itself in avoidance behavior that was quantified by our behavioral tasks in the first study. In the next study we wanted to know how ‘strong’ avoidance behavior affects the three tasks’ readouts, how participants with specific phobia behave in presence of the feared stimulus and how this behavior is related to the intensity of their fear. By replacing the fear conditioned stimuli with any other object or animal, our three behavioral tasks of the preceding study also provide the possibility to investigate behavior towards any object. In the second paper of my thesis (Binder et al., 2022), we used spider phobia as casus belli of specific phobia, because this is the most common specific phobia in Germany: Spiders are strongly disliked by up to one third of the population (Davey, 1991; Muris et al., 1997) with females being five times more frequently affected than males (Fredrikson et al., 1996). Correspondingly, the fear conditioned stimuli were replaced by a spider as the phobic stimulus and a turtle as neutral stimulus. We hypothesized that participants would avoid the spider in all behavioral tasks and that quantification of avoidance would be correlated with fear intensity.

We studied 31 female participants, including 15 spider-phobic and 16 non-phobic individuals. Beside the goal of characterizing fear behavior of phobic patients in more detail and to examine the sensitivity of these tasks to assess avoidance behavior, there was another difficulty: The confrontation with the phobic animal is always highly upsetting and challenging for phobic patients. One might assume that it would be easier in iVR, as there are no real animals and thus additional coping strategies such as closing the eyes or reminding oneself that it is not real are feasible and effective. However, meta-analyses have shown that VR exposure is as effective as real exposure (Carl et al., 2019), suggesting that exposure in VR may be as intense as in reality. Accordingly, we optimized the fully automatized iVR procedure for this purpose and used the study to verify the feasibility of the procedure for phobics.

We found six characteristic behaviors that differentiated the groups:

- *Distance*: Phobics kept a larger distance to the spider than to the neutral stimulus in the search task.
- *Choice*: Phobics preferred the path with the neutral stimulus instead of the one with the spider, even if it was longer.
- *Duration*: Phobics took more time to touch the spider than to touch the turtle.
- *Eye gaze*: Phobics watched the spider more frequently and longer than the neutral stimulus.
- *Body orientation*: Phobics oriented their whole body more towards the spider.
- *Hesitation*: The fluentness of the hand-motion was lower when touching the spider compared to the neutral stimulus.

Beside these behavioral characteristics we also observed differences in heart rate and pupil size. However, the physiological effects were comparatively small and could not be detected in all behavioral tasks, as varying illuminance and participants' activity disturbed the effects.

The phobics strongly disliked the virtual spider and showed consistent avoidance behavior in all behavioral tasks manifest in the six characteristic behaviors. However, the non-phobics were rather heterogeneous in respect of the intensity of their fear of spiders. Therefore, we used the fear of spider questionnaire score to subdivide the non-phobics into fearfuls and non-fearfuls to examine these differences. The fearfuls showed avoidance behavior dependent on the behavioral task and the non-fearfuls showed no avoidance behavior in any task. Although some participants had very strong fear of spiders, all participants successfully handled the procedure. Even in the behavioral approach task, in which they had to touch the spider, all phobics did so. Although some took three minutes longer to touch the spider than to touch the neutral animal.

A further interesting finding in this study was the central role of spider valence. The perceived valence of the spider by the participant was correlated with all behavioral tasks, subjective wellbeing after the experiment, and the fear of spider questionnaire score. Partial correlation analyses indicated that spider valence mediated the effect of general fear of spiders on fear behavior and subjective well-being after exposure.

1.4 Conclusion and outlook

In this dissertation I presented a fully automated iVR procedure for use in research on generic fear processes in healthy subjects and in research on pathological fear. The procedure provides several behavioral readouts of fear. The diverse quantification allows an automated and precise adjustment of the intensity of exposure in therapy. In this extent, we contributed to an automated, accepted, and efficient assessment of specific phobia, with potential relevance for exposure treatment. With such a treatment, the effort of expensive therapists can be reduced to enhance its scalability and to make therapy available to a broader range of people (Freeman et al., 2018). Furthermore, the presented importance of spider valence could be used to facilitate exposure by first taking a spider with a less negative valence and successively making it more unpleasant.

In the phobia study, we observed that phobics touched the spider already quicker the second time than the first time. In an unstructured interview after the experimental procedure, the phobics explained that they already knew in the second trial what the spider would be doing when it is touched, namely nothing. This effect of increased predictability is consistent with the cognitive vulnerability model, according to which predictability, along with controllability and dangerousness, has an effect on spider fear (Armfield, 2006, 2007). In addition, it showed the important role of cognitions in fear and raised the question what else the phobics were thinking during exposure? According to Arntz, Lavy, van den Berg, and van Rijsoort (1993), frequent thoughts in individuals with spider phobia are that the spider “comes towards me”, “jumps onto me”, or “crawls into my clothes”. As the spider in our experiment showed defensive behavior to the touch by retreating, shrinking, and freezing, these thoughts proved to be wrong and thus might have decreased fear. Cognitions appeared to play a role not only in the second but also in the first study, in which some participants reported that they developed individual hypotheses about the relation between the CS, the US, and their behavior. Consequently, their behavior was influenced by testing behavior to examine their hypotheses, sometimes leading to approaching the CS+ to see if another shock would still follow. In this way, our results showed the importance of cognitions in the process from stimulus over emotion to behavior: Cognitions are also triggered by the stimulus, have a bidirectional relation with emotions, and have a direct influence on behavior. In this regard, the bidirectional relation between cognitions and emotions appears to be essential in anxiety disorders, and this experimental procedure can help us to understand it.

With the fear conditioning study, we also contributed to the ongoing debate on the development of avoidance behavior (Krypotos et al., 2015) by showing that Pavlovian fear conditioning can be sufficient to induce avoidance. However, the observed avoidance behavior was weak. Only after additional reinforcement, avoidance behavior could be detected in all behavioral tasks. In the context of this debate, the question arises how this additional reinforcement should be interpreted. Was it instrumental conditioning? Arguments in favor are that it occurred during the behavioral tasks, that approaching the CS+ was followed by the US, and that avoiding the CS+ led to the absence of the US. This implies that both, the occurrence of the US and the absence of the US, could have served as reinforcer. However, “approaching” and “avoiding” varied between the tasks, were rather generic and were no specific behaviors that could have been reinforced. An alternative explanation could be that despite the high reinforcement rate, uncertainty of the occurrence of the US was still high. Additional reinforcement may have reduced uncertainty and thus strengthened the fear. Although participants’ comments in the unstructured interview after the experiment support this interpretation, our data cannot confirm this explanation either. Nevertheless, the presented behavioral tasks to quantify avoidance behavior are well suited for studying the mechanisms of the development of avoidance behavior. For example, an instrumental conditioning task could be added instead of or after the fear conditioning task to investigate the role of instrumental conditioning in more detail. To test the habituation hypotheses of LeDoux et al. (2017), the tasks could be presented repetitive in one or multiple sessions dependent on how one defines habituation. In this way, new evidence of human behavior can be generated to advance the debate.

In summary, it was demonstrated in healthy participants that Pavlovian fear conditioning is sufficient to produce mild avoidance behavior that is detectable by the behavioral search task, but that additional reinforcement is required to strengthen the avoidance behavior and make it detectable in the behavior approach task. For participants with specific phobia, strong avoidance behaviors were observed that were related to subjective fear report and manifested in distance, choice, duration, gaze, hesitation, and body orientation in all behavioral tasks. Overall, this dissertation demonstrated that iVR is useful in fear research and presented three new tasks for studying fear. The results contributed to the understanding of the development of fear and may open new automated treatments for anxiety disorders.

2. Paper I

Binder, F. P., & Spoormaker, V. I. (2020). Quantifying Human Avoidance Behavior in Immersive Virtual Reality. *Frontiers in Behavioral Neuroscience*, *14*. https://doi.org/10.3389/fnbeh.2020.569899

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Quantifying Human Avoidance Behavior in Immersive Virtual Reality

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Avoidance behavior is a key symptom of most anxiety disorders and a central readout in animal research. However, the quantification of real-life avoidance behavior in humans is typically restricted to clinical populations, who show actual avoidance of phobic objects. In experimental approaches for healthy participants, many avoidance tasks utilize button responses or a joystick navigation on the screen as indicators of avoidance behavior. To allow the ecologically valid assessment of avoidance behavior in healthy participants, we developed a new automated immersive Virtual Reality paradigm, where participants could freely navigate in virtual 3-dimensional, 360-degrees scenes by real naturalistic body movements. A differential fear conditioning procedure was followed by three newly developed behavioral tasks to assess participants' avoidance behavior of the conditioned stimuli: an approach, a forced-choice, and a search task. They varied in instructions, degrees of freedom, and high or low task-related relevance of the stimuli. We initially examined the tasks in a quasi-experiment (*N* = 55), with four consecutive runs and various experimental adaptations. Here, although we observed avoidance behavior in all three tasks after additional reinforcement, we only detected fear-conditioned avoidance behavior in the behavioral forced-choice and search tasks. These findings were largely replicated in a confirmatory experiment (*N* = 72) with randomized group allocation, except that fear-conditioned avoidance behavior was only manifest in the behavioral search task. This supports the notion that the behavioral search task is sensitive to detect avoidance behavior after fear conditioning only, whereas the behavioral approach and forced-choice tasks are still able to detect "strong" avoidance behavior after fear conditioning and additional reinforcement.

Keywords: anxiety, fear conditioning, avoidance, virtual reality, reinforcement, BAT, forced-choice, search task

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INTRODUCTION

Avoidance behavior is a key symptom of most anxiety disorders (American Psychiatric Associaton, 2013) and a central readout in animal research (Lonsdorf et al., 2017). There are numerous well-established tests to assess fear-related behavior in animals (Bailey and Crawley, 2008). In humans, the objective quantification of overt avoidance behavior is typically restricted to clinical populations. In the behavioral approach test (Grös and Antony, 2006), for example, individuals with a specific phobia have to approach the phobic stimulus whereby the distance to it functions as primary readout. Naturally, this test is only effective for intense fear, such as in phobia.

To measure more moderate fear in a healthy sample, other methods are required to quantify avoidance behavior. In laboratory settings, human avoidance behavior is currently assessed by questionnaires or computer-based tasks, during which button presses or a joystick navigation on the screen serve as measurement of behavior. This has provided valuable insights, for example, into the mechanisms of avoidance learning (Pittig et al., 2020), the effect of cost of avoidance (Rattel et al., 2017), or sex differences (Sheynin et al., 2014). Due to their experimental nature, avoidance tasks to date are primarily focused on avoiding the aversive event. However, anxiety disorders are characterized by the avoidance of the antecedent stimulus (i.e., the spider) and not necessarily the aversive event only (i.e., the bite of a spider). In order to reflect this characteristic, we need more experimental paradigms that investigate the avoidance of the antecedent stimulus (Krypotos et al., 2015). Furthermore, we need more ecologically valid and sophisticated designs that model ambiguity and conflict to fully understand the pathological mechanisms of avoidance in anxiety disorders and optimize treatment (Beckers et al., 2013; Pittig et al., 2018).

The recent technological development of immersive Virtual Reality (iVR) allows the objective tracking of human behavior with high precision in experimentally designed virtual contexts. These contexts are generated by a computer and presented to the participant in a sufficiently convincing manner to suspend disbelief and to become fully engaged with the context. Navigation is more natural as participants can walk around and grab objects intuitively. All motions can be recorded using sensors on the torso and limbs and can be extended with simultaneous subjective or physiological readouts, such as ratings or heartrate. Compared to experiments in real contexts, experiments in iVR can be fully automated yielding a high level of standardization. Finally, participants can be easily transferred from one context to another. The potential of this technology has been shown, for example, in the study of Biedermann et al. (2017). They translated the elevated plus-maze to iVR, in which participants walked on a wooden plus-shaped maze with two closed arms being surrounded by rocks and two open arms being in the air. They observed that participants with high trait anxiety spent less time walking on the open arms than participants with low trait anxiety. Studying behavior with such an integrated set-up could help us translate preclinical findings to humans and expand our understanding of human avoidance behavior. Ultimately, the quantification of avoidance behavior might be beneficial for monitoring the progress of exposure treatment in patients.

The question is, how can avoidance behavior be experimentally induced in healthy participants? In animal research, a well-established model to induce fear-behavior is fear conditioning (Milad and Quirk, 2012; LeDoux et al., 2017). It entails the repeated pairing of a neutral stimulus with an intrinsically aversive event, such as a mild electrical shock. The former neutral stimulus is called the conditioned stimulus (CS+) and the aversive event is the unconditioned stimulus (US). In a differential Pavlovian conditioning paradigm another stimulus is added, which is never followed by the US, resulting in a safety stimulus (CS−). In line with animal work, previous work in humans has revealed that approach/avoidance tendencies manifest after fear conditioning in computer-based tasks, with a joystick or button press (Cornwell et al., 2013; Krypotos et al., 2014; Rattel et al., 2017).

Initial work has shown that fear conditioning is effective using iVR (Kroes et al., 2017). This study used a procedure where participants were sitting on a chair and were automatically navigated on a predefined path through virtual rooms. This was necessary to exclude idiosyncratic behavior during conditioning. They observed reliable acquisition of subjective fear (arousal and valence), physiological fear responses (electromyography startle responses, and skin conductance responses) and showed iVR to be an effective tool to investigate human contextual processes. This study raises the question of how participants would behave in such a context, if they had more degrees of freedom or if avoidance had been made less explicit, as this could affect the sensitivity of the tasks.

To investigate these questions, we developed a new procedure in iVR, in which differential fear conditioning was followed by three tasks to assess the behavior of participants towards the conditioned stimuli: a behavioral approach task with the aim to translate the behavioral approach task to healthy human participants by instructing them to touch the CS+ and CS-; a forced-choice task, in which participants chose between a path alongside the CS+ or a path alongside the CS-; a behavioral search task, in which participants could move freely within a squared area with the CSs presented on opposite sides, and a gaming component to induce movement. These three tasks allowed us to compare varying instructions, degrees of freedom and high or low task related relevance of the stimuli on the sensitivity of the task to detect avoidance behavior. Furthermore, the manipulation of the order of the behavioral tasks enabled us to investigate the effect of additional reinforcement in previous tasks on avoidance behavior in the test task. In this article we present two experiments: An exploratory quasi-experiment to explore initial effects and a second confirmatory experiment with randomized group allocation to test the robustness of the effects.

QUASI-EXPERIMENT

Materials and Methods

Participants and Runs

A total of 60 healthy individuals participated in the four runs of the quasi-experiment. They were recruited through a variety of means including a notice at local universities and advertisements on the institute's website and on social media. We excluded 5 participants: 1 participant misunderstood the instructions, 3 participants reported after the experiment that they had not learnt the CS-US contingencies, and 1 participant did not see the balloons during the behavioral tasks. A total of 55 participants (M = 24.3, SD = 4.2, range: 18–34, female: 30) were included in the analyses. The measurements took place in the afternoon between noon and 6 p.m. The study protocol was approved by a local ethics commission (Faculty of Medicine at Ludwig Maximilian University of Munich; project number: 18–403) and was conducted in accordance with the Declaration of Helsinki (2013).

The quasi-experiment consisted of four different runs. In each run, a group of participants underwent the experiment with the same protocol. Afterward, a few manipulations on the protocol were made for the next run. See **Supplementary Table 1** for a detailed description of all manipulations.

Setup

The VR was generated in Unity 3D Pro (version 2018.3) with a sampling rate of 90 frames per second. We used the HTC Vive with controllers and in-ear headphone to present the VR, which was connected to Steam VR.

Participants were free to move around the laboratory (room of 4.6 m × 5.5 m), which spatially agreed with the virtual scenes: three sides were aligned with the respective wall; one side was shortened because of the desk with the desktop computer, resulting in a field of 4.6 m × 4.3 m. In order to increase the participant's sense of presence, we deactivated the chaperone, which is a safety grid in the virtual environment indicating the border of the field. Instead, the borders of the field were indicated as walls, wood blanks, or cordons. The cable of the HTC Vive was held by a trained person to ensure participants could move freely.

Electrocardiography was measured with the one channel eMotion Faros 180 device from BioSign. It was connected via Bluetooth to the computer, operated in online mode, and recorded with 250 samples per second. The Faros device was synchronized with Unity at startup. From this point on, package numbers of the received data were used to determine the time of the signal. This ensured that communication delays, due to buffering in the Bluetooth connection, did not affect data quality.

The body motion data was recorded with the Perception Neuron V2 System using 18 sensors on the torso, limbs, and head. It was wirelessly transferred to the Axis Neuron software (version 3.8.42.6503), where the accelerations of the sensors were converted in directed positions of 25 human body parts. The Perception Neuron Unity-Plugin (version 0.2.11) received these positions and used them to animate the default Perception Neuron avatar, which represents the body of the participant. We ignored the position in the room from the motion tracking system and instead used the precise position of the head-mounted display (HMD), to which we fixed the head of the avatar. With that we eliminated the global drift, which is a well-known error in inertial motion tracking systems, induced by the many summations of the acceleration over time (Lopez-Nava and Munoz-Melendez, 2016). The size of the avatar was adjusted to fit the body size of the participant. All motions were recorded in Unity by saving the global position and rotation of all 25 body parts of the avatar in every frame.

We used the PsychLab SHK1 constant current shocker (60 Hz AC) for 100 ms-duration electrical shocks (0.8–5 mA), as performed by Schmitz and Grillon (2012). It was connected to the computer via USB and was controlled directly from Unity. The electrode cable was extended by a 10 m custom produced cable of the manufacturer. The two electrodes were mounted to a piece of leather to fix the center distance to 2 cm.

Procedure

In the announcements, interested participants were asked to send an e-mail to apply for participation. The response of this mail contained a link to an online questionnaire covering the inclusion/exclusion criteria. Eligible participants were immediately redirected to a webpage on which they could choose their preferred timeslot of participation. One day before the experiment, they received a reminder of their appointment including a link to an online questionnaire that had to be filled out before the experiment. It consisted of Trait Anxiety (Spielberger, 1983), Big Five Inventory (Rammstedt and Danner, 2017), Intolerance of Uncertainty (Gerlach et al., 2008), Short Resilience Scale (Leppert et al., 2008), Beck-Depression Inventory II (Kühner et al., 2007), Motion Sickness Susceptibility Questionnaire revised (Golding, 1998), Anxiety Sensitivity Index 3 (Kemper et al., 2009), Sensation Seeking Scales, Form V (Beauducel et al., 2003), and the CID-Screener (Wittchen et al., 1999).

When participants arrived in the laboratory, they were informed about the procedure and gave their written informed consent. The two electrodes (55 mm; Ag/AgCl pre-gelled) for the electrocardiography were attached under the right collarbone and on the lower left ribs. The electrodes for the electrical shocks were attached to the left calf with an elastic bandage. The motion tracking sensors were placed and calibrated according to sex and body size, following the guidelines in Axis Neuron. The participant put on the head mounted display and the experiment started.

After the experiment, all sensors were detached and participants received a tablet device on which they rated their general anxiety in VR (VAS), US intensities, CS valences, evaluation of the duration in VR, nervousness at the beginning of the experiment, and filled out a few additional questionnaires: the Simulator Sickness Questionnaire (Kennedy et al., 1993), and the Presence Questionnaire Version 3 (Witmer et al., 2005).

Virtual Scenes

The first scene was the Tutorial, which was already loaded before the participant put on the HTC Vive. After the start of the experiment all (pre-recorded) instructions ran automatically. The Tutorial was followed by the Fear Conditioning task and the experiment continued with the three behavioral tasks in a counter-balanced but predefined task sequence. The experiment ended with the Recall task.

Tutorial

The Tutorial was a room, like the laboratory. It served to habituate participants to VR and to familiarize them with the VR-interaction. At the beginning, they received the instruction that they can move around as they would in the real world and should not walk through virtual objects or walls, as these could be covered by real ones. The controller was explained, and its handling rehearsed. The participant walked through the whole room once. The collection, carrying and dropping of objects was explained and trained. The shock intensity was also calibrated (Schmitz and Grillon, 2012). The occurrence of a shock during calibration was indicated by a 2 s countdown on a monitor on the wall. The intensity of the first shock was zero (no shock) in order to familiarize them with the procedure before the first real shock occurred. Afterward participants were asked to rate the intensity of the shock on a 5-point Likert scale (anchored with 1 = hardly noticeable, 2 = noticeable, 3 = unpleasant, 4 = very unpleasant, 5 extremely unpleasant). If they rated 1–3 the intensity was increased by one step of 0.82 mA and another shock was presented. This increment was chosen as it reached the maximum 5 mA with six equally sized small steps. If the participant rated the intensity as 5, the shock was decreased by a third of a step (0.27 mA). When they rated the shock as 4 the calibration was over, and this intensity was used for the rest of the experiment.

Fear Conditioning

During the Fear Conditioning task (see **Figure 1A**) participants sat on a chair in an open square. The CSs were green and blue balloons, which were inflated out of a vase, 6 m in front of the participant. They floated for 8 s toward the participants and then passed them by. The inter-trial-interval was set to 9 s. One of the balloons (CS+) was followed by the US after 6 s in 80% of trials, when the balloon was in closest proximity to the participant. The other colored balloon (CS-) was never paired with the US. The CS-type to balloon-color relation was counter-balanced between participants. Participants were instructed that this is a learning task, in which various balloons are shown and unpleasant stimuli can occur and that their job is to find out what will happen and when. In a short habituation phase, both balloons were presented two times each, without US. Afterward, a large monitor emerged from the ground and each CS was presented together with the question for the rating: "How likely does an electrical shock occur?" Participants rated their US probability on a Likert scale with eleven steps from 0 to 100%. After the habituation phase, participants were informed that from now on unpleasant stimuli can occur and at the very first rating they should simply guess. The subsequent fear acquisition contained two blocks in which both CSs were presented five times each, in a pseudorandom order. Between these blocks, as well as at the beginning and at the end of these blocks, ratings took place. After the acquisition phase participants were asked to stand up. They received the instruction that in all following tasks the unpleasant stimuli may occur again, before the next worlds were loaded.

Behavioral Approach Task ("Touch the Enemy")

In this task (see **Figure 1B** and **Supplementary Video 1**), participants were instructed to touch the floating CS on the other side of the room, which was tied to the floor and not moving. After a countdown period of 10 s, participants had to walk across the room and to touch the CS with their right hand. This was done for each CS twice, in alternating order. The type of CS presented first was counter-balanced between participants.

Behavioral Forced-Choice Task ("Path-Choice")

In Path-Choice (see **Figure 1C** and **Supplementary Video 2**), the task was to collect a book from the counter on the opposite side of a reception area in a lobby and place it in the rack on the backside, where participants had started. A large table stood in the center of the room to force participants to pass it either on the left or on the right side. One of the CSs was presented on each side of

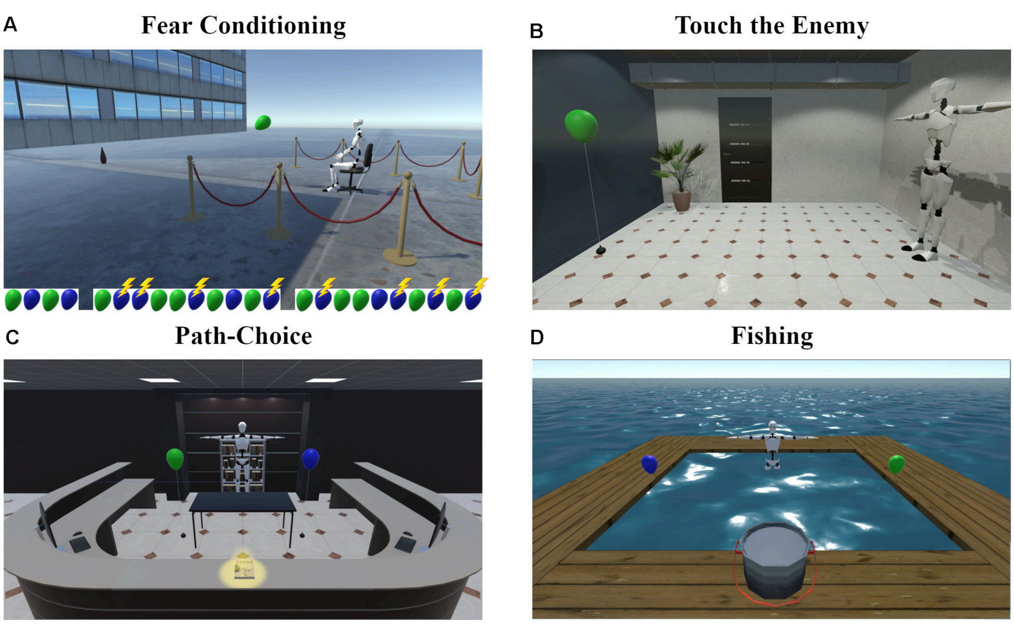

FIGURE 1 | Screenshots of the virtual scenes for **(A)** Fear Conditioning and Recall, **(B)** Touch the Enemy, **(C)** Path-Choice, and **(D)** Fishing. The balloon sequence in **(A)** represents the trial order during habituation and both fear acquisition blocks with green representing the CS− and blue the CS+. Reinforced trials are marked with a flash. Note that the 2D screenshots do not convey the 3D-360 degree view that participants encountered in iVR. The screenshots are depicted from an allocentric standpoint for illustration purposes only. Participants experienced all scenes in the first-person view and were always able to move freely by naturalistic body movements.

the table, this way participants were forced to choose between passing the CS+ or CS- when crossing the room. There were five trials: After a book was put in the rack, the next one appeared. The first book was placed in the center of the counter with both paths having the same length. The other books were placed on the right (book 2), on the left (book 3), on the far right (book 4), and on the far left (book 5). The position of the CS+ (left or right) was counterbalanced between participants and the CSs swapped after book 1 and book 3 occurred.

Behavioral Search Task ("Fishing")

Participants stood in hip deep, non-transparent water and were instructed to try to catch fishes with a hand-net (handle length: 0.75 m, net diameter: 0.40 m) in their right hand (see **Figure 1D** and **Supplementary Video 3**). The field was surrounded by a wooden walkway and participants were told to stay within it. The start position was in the middle of the long side, facing at the field. The two CS+ and CS− were floating in the wind and tied to the short left and right sides of the wooden walkway. The placements of the CSs were counterbalanced between participants. Participants were informed that they cannot see where the fish are, this way we kept them unaware of the absence of fish in the water. Lastly, after 2 min of fishing, regardless of the participant's position, if the hand-net was in the water for more than 0.5 s, one fish was automatically placed in the net and the controller vibrated, indicating the success. Finally, participants were told to drop the fish in the pot on the walkway.

Recall

The Recall task was in the same context as the Fear Conditioning task (see **Figure 1A**), but differed from it in five aspects: (1) There was another explanation at the beginning, saying that the task is the same as before, only shorter. (2) There was no habituation phase. (3) Both types of CSs were presented four times each. (4) CS presentations were not reinforced anymore. (5) Ratings were only acquired at the beginning and at the end of the task.

Statistical Analyses

All analyses were performed in Matlab R2019b and figures were generated with the "Gramm" toolbox (Morel, 2018). The η^2 for analyses of variance (ANOVA), the Glass' Δ for two sample t-tests, Hedges' g_1 for one sample t-tests, and Cohen's U3 for Mann-Whitney U-tests were calculated with the Matlab-toolbox "Measures of Effect Size" version 1.6.1 (Hentschke and Stüttgen, 2011). For repeated measure analyses of variance (rmANOVA), we calculated the partial-eta-squared (η_p^2) and generalized-eta-squared (η_G^2) (Olejnik and Algina, 2003; Bakeman, 2005) effect sizes.

Heart rate analyses

The PhysioNet-Cardiovascular-Signal-Toolbox (version 1.0.2; Poian et al., 2019) was used to detect R-peaks in the electrocardiography-signal. RR-Intervals were calculated as differences between successive peaks and related to the time of the second peak. The resulting RR-timeseries was linearly interpolated with a sampling rate of 250 samples per second and all values higher than 1.5 s were marked as missing.

Task specific grouping: temporal-position and CS+-Experience

The *temporal-position* is a task specific partitioning of participants based on the individual position of the task in the task sequence. The temporal-position one, two, and three contain all participants who had the specific task as first, second, or last behavioral task, respectively.

To investigate the effect of additional reinforcement on avoidance behavior, we defined the *CS+-Experience* as categorization of possible manipulations of the CS-US contingency after the Fear Conditioning task, but before the respective task. Participants from temporal-position two or three were assigned to exactly one of these mutually exclusive categories: *no-approach* means the participant had the chance, but never approached the CS+ in any preceding task; *reinforcement* means the participant approached the CS+ at least once and every approach was reinforced; *non-reinforcement* means the participant approached the CS+ at least once and the approach was never reinforced; *mixed-reinforcement* is a mix of reinforcement and non-reinforcement and means the participant approached the CS+ at least twice, where at least one approach was reinforced and at least one was not. This categorization was also task specific: For instance, a participant with the order Touch the Enemy, Fishing, and Path-Choice could be in the category reinforcement for the Fishing task, but in the category mixed-reinforcement for the Path-Choice task, if there was an unreinforced approach during the Fishing task. Effects of the CS+-Experience were tested by the task dependent ANOVA or Kruskal-Wallis test with all participants from temporal-position one and participants from categories reinforcement, non-reinforcement, and mixed-reinforcement. Participants of the category no-approach were excluded from the analysis of the CS+-Experience as they never approached the CS+ and therefore did not receive additional (non-)reinforcement.

Fear Conditioning and Recall

Subjective ratings were analyzed with a rmANOVA with stimulus and time as within factors.

The RR-change is the trial-wise readout based on the interpolated RR-timeseries. For that, we defined the baseline as the 5 s interval before stimulus onset. The RR-change was calculated as difference between the RR-value at 6 s after stimulus onset and the mean of the baseline. This readout was analyzed with a rmANOVA with stimulus and time as within factors. Due to missing data after technical problems with the device, we excluded five participants from the heart rate analyses within the Fear Conditioning and nine from the Recall task.

Touch the Enemy

The readout was calculated as the difference between the time to touch the first CS+ and the time to touch the first CS−. The time to touch was defined as the time from the end of the countdown until touching the CS by hand. Effects of temporal-position or CS+-Experience were tested with an ANOVA, one-sided one sample t-tests were used to test single groups for avoidance and independent t-tests were used for *post hoc* comparisons of the temporal-position one to the CS+-Experience categories. In this analysis we excluded four participants: one was starting before the countdown, one was running, one was an extreme outlier (time to touch > 15 s), and one lost the equipment during the task.

Path-Choice

For Path-Choice we counted the number of CS- passes before the first CS+ approach. A CS+ approach was defined as the participant passing the CS+, regardless of whether the participant continued walking or turned around and took the CS- path (which happened a few times only). With two directions (there and back) per trial and five trials in total, values between 0 and 10 are possible, where 0 means a CS+ approach at the very beginning and 10 means no CS+ approach at all. This readout is independent of whether the CS+ approach was reinforced or not. Since this results in a geometric distribution, the Kruskal-Wallis test was used to test for effects of temporal-position or CS+-Experience. We used the one-sided binomial test on the very first pass (readout > 0 or not) to test single groups for avoidance and the Mann-Whitney U-test for *post hoc* comparisons of the temporal-position one to the CS+-Experience categories.

Fishing

The readout of Fishing was defined as whether the participant started on the CS- or CS+ side and how long the participant stayed on that side. In order to make that robust against back and forth jumping on a single centered threshold, we defined a small, neutral band of approximately 1 m width in the middle between CS− and CS+ and analyzed at which side of the band the participant left. For this we calculated the difference between the distance from the participant to the CS+ and to the CS−. A difference of zero means equal distances to both stimuli and the participant was located on the bisecting line between them. If it exceeded the threshold of 1 m first, we defined it as avoidance behavior and measured the time until it was below −1 m. If it fell below −1 m first, we called it approach behavior and measured the time till it was above 1 m. To be able to distinguish between these two cases, we defined the approach-avoid time to be positive in the avoidance case and negative in the approach case. This definition leads to a symmetrically, but not normally distributed readout and the Kruskal-Wallis test was used to test for effects of temporal-position or CS+-Experience. To test single groups for avoidance, we also used the one-sided binomial test (readout > 0 or not) and the Mann-Whitney-U-test was used for *post hoc* comparisons of the temporal-position one to the CS+-Experience categories. In this analysis we excluded one participant due to misunderstanding the instructions, as reported in the interview after the experiment.

Across Tasks Analyses

The Friedman test (Friedman, 1937) was used to test for an effect of participant over all tasks. Similarly, we defined the *Rank-Sum* as the within participant over tasks sum of the within task over participants ranks and used it as measure for overall avoidance. We calculated the Spearman correlation between the tasks, the Rank-Sum, and questionnaires. Only correlations with uncorrected $p < 0.05$ are reported. A subsequent correction for multiple testing was performed with the Bonferroni procedure (corrected threshold: 0.05/(33*4) = 0.00038). Sex differences were tested with the Mann-Whitney U-test. In these analyses, we excluded five participants which had been excluded in the analyses of any of the behavioral tasks, resulting in 50 participants (M = 24.4, SD = 23.5, range = 18–34, female: 27).

Results

Mean electrical shock current was 3.1 mA (SD = 1.2 mA). Participants rated it after the experiment as unpleasant (M = 6.3, SD = 1.4, scale = 1–10). As shown in **Figure 2**, participants reported high presence in the Presence Questionnaire 3 ($M \pm SD$): involvement, 5.4 ± 0.7; sensory fidelity, 5.1 ± 1.0; adaptation immersion, 5.9 ± 0.5; interface quality, 2.1 ± 0.8. Moreover, they reported only slight side effects in the Simulator Sickness Questionnaire: total score, 14.3 ± 14.8; nausea, 11.4 ± 12.5; oculomotor symptoms, 10.7 ± 13.1; disorientation, 16.7 ± 22.3.

Fear Conditioning and Recall

The shock expectancy ratings during the Fear Conditioning and Recall tasks are shown in **Figures 3A,B**, respectively. The analyses revealed a significant stimulus effect [$F(1, 54) = 1083.8$, $p < 0.001$, $\eta_p^2 = 0.95$, $\eta_G^2 = 0.80$], a time effect [$F(2, 108) = 3.39$, $p = 0.04$, $\eta_p^2 = 0.06$, $\eta_G^2 = 0.02$], and a stimulus × time interaction [$F(2, 108) = 379.0$, $p < 0.001$, $\eta_p^2 = 0.88$, $\eta_G^2 = 0.71$] during fear conditioning and a stimulus effect [$F(1, 54) = 300.72$, $p < 0.001$, $\eta_p^2 = 0.85$, $\eta_G^2 = 0.66$], a time effect [$F(1, 54) = 436.55$, $p < 0.001$, $\eta_p^2 = 0.89$, $\eta_G^2 = 0.60$], and a stimulus × time [$F(1, 54) = 270.29$, $p < 0.001$, $\eta_p^2 = 0.83$, $\eta_G^2 = 0.54$] interaction during recall.

The RR-changes during the Fear Conditioning and Recall tasks are shown in **Figures 3C,D**, respectively. The analyses revealed a stimulus effect [$F(1, 49) = 13.63$, $p < 0.001$, $\eta_p^2 = 0.22$, $\eta_G^2 = 0.02$], a trial effect [$F(9, 441) = 3.12$, $p = 0.001$, $\eta_p^2 = 0.06$, $\eta_G^2 = 0.02$], and a stimulus × trial interaction [$F(9, 441) = 2.29$, $p = 0.02$, $\eta_p^2 = 0.04$, $\eta_G^2 = 0.02$] during fear conditioning. None of the factors stimulus [$F(1, 45) = 0.03$, $p = 0.86$, $\eta_p^2 = 0.00$, $\eta_G^2 = 0.00$] and trial [$F(3, 135) = 1.21$, $p = 0.31$, $\eta_p^2 = 0.03$, $\eta_G^2 = 0.01$] or the interaction stimulus × trial [$F(3, 135) = 1.61$, $p = 0.19$, $\eta_p^2 = 0.03$, $\eta_G^2 = 0.01$] were significant during recall.

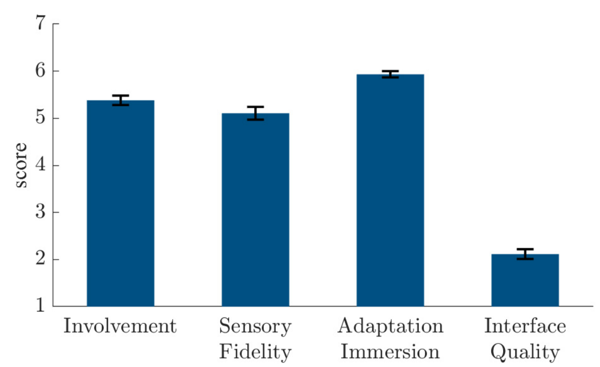

FIGURE 2 | Presence Questionnaire 3 (Witmer et al., 2005) scores in the **quasi-experiment**.

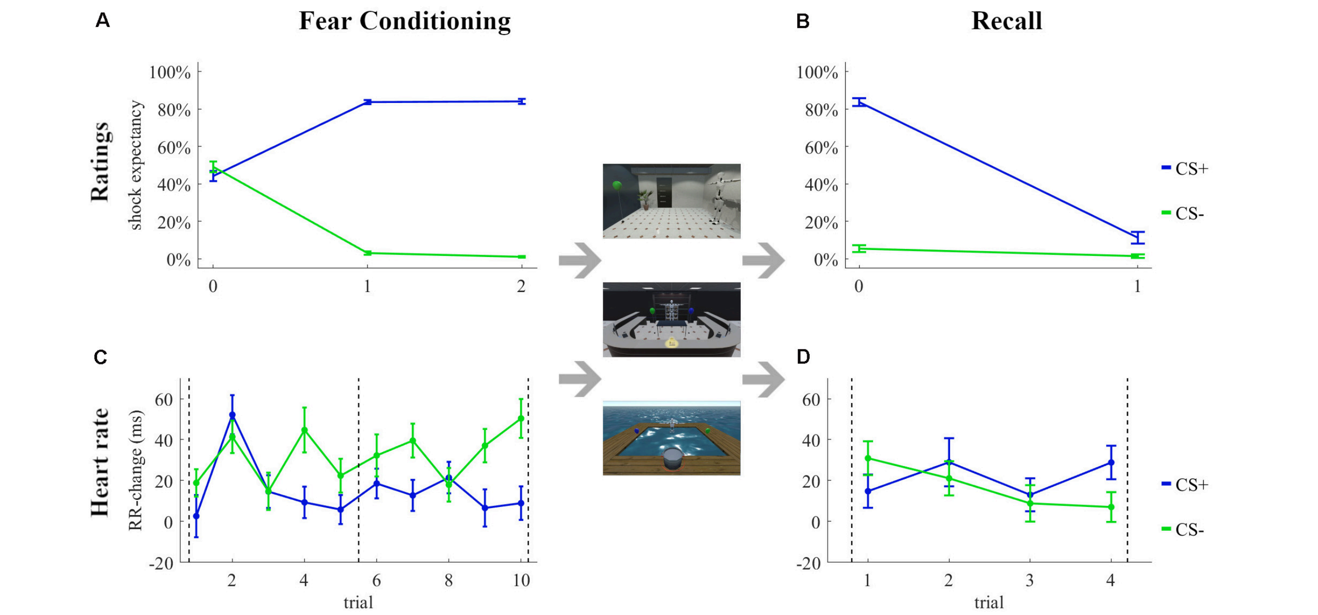

FIGURE 3 | Subjective ratings **(A,B)** and changes in heart rate **(C,D)** during the Fear Conditioning **(A,C)** and Recall **(B,D)** tasks in the **quasi-experiment**. Rating 0 was the first subjective rating before the first trial. Dashed lines in **(C,D)** indicate the subjective ratings.

Touch the Enemy

The time to touch difference increased with rising temporal-position (see **Figure 4A**), but our ANOVA revealed no significant effect of temporal-position [$F(2, 48) = 0.55$, $p = 0.58$, $\eta^2 = 0.02$]. Single temporal-position analyses revealed no significant avoidance for temporal-position one [$t(17) = 1.45$, $p = 0.08$, $g_1 = 0.34$], but an effect for temporal-position two [$t(13) = 1.79$, $p = 0.05$, $g_1 = 0.48$] and three [$t(18) = 2.40$, $p = 0.01$, $g_1 = 0.55$], see **Figure 4B** for the distribution of the readout for temporal-position one. The ANOVA revealed no effect of CS+-Experience [$F(2, 45) = 0.77$, $p = 0.47$, $\eta^2 = 0.03$, see **Figure 4C**]. One sample t-tests showed no effect for non-reinforcement [$t(8) = 1.14$, $p = 0.14$, $g_1 = 0.38$] and no-approach [$t(2) = 2.11$, $p = 0.08$, $g_1 = 1.22$], by contrast, we observed a significant difference from zero for reinforcement [$t(20) = 2.31$, $p = 0.02$, $g_1 = 0.50$].

Path-Choice

The Kruskal-Wallis test revealed no effect of temporal-position [$X^2(2, N = 55) = 1.31$, $p = 0.52$]. As shown in **Figure 4D**, there was avoidance behavior in temporal-position one ($p = 0.001$, $N = 26$, 21 avoiders), and two ($p < 0.001$, $N = 25$, 21 avoiders), but not if Path-Choice was the last task ($p = 0.31$, $N = 4$, 3 avoiders). **Figure 4E** shows that 5 out of 26 participants with Path-Choice as first behavioral task directly approached the CS+, the others avoided the CS+ at least once. The grouping by the CS+-Experience shows no effect of additional reinforcement on avoidance behavior [$X^2(1, N = 50) = 0.05$, $p = 0.82$, see **Figure 4F**]. The binomial tests on single CS+-Experience categories showed an effect for reinforcement ($p < 0.001$, $N = 24$, 20 avoiders), but not for no-approach ($p = 0.19$, $N = 5$, 4 avoiders).

Fishing

Analyses of Fishing also revealed no effect of temporal-position [$X^2(2, N = 54) = 4.93$, $p = 0.09$]. As shown in **Figure 4G**, there was avoidance behavior in temporal-position one ($p = 0.01$, $N = 10$, 9 avoiders), and two ($p = 0.004$, $N = 15$, 13 avoiders), but not if it was the last task ($p = 0.07$, $N = 29$, 19 avoiders). Nine out of ten participants with Fishing as first behavioral task avoided the CS+ (see **Figure 4H**). The grouping by the CS+-Experience (see **Figure 4I**) shows no effect of additional reinforcement on avoidance behavior [$X^2(2, N = 53) = 1.88$, $p = 0.39$]. The binomial tests on single CS+-Experience categories showed an effect for reinforcement ($p = 0.001$, $N = 32$, 25 avoiders), but not for mixed-reinforcement ($p = 0.50$, $N = 11$, 6 avoiders) and no-approach ($p = 0.50$, $N = 1$, 1 avoiders). The temporally dynamic analysis showed that avoidance behavior was confined to the first twenty seconds (see **Figure 5**).

Across Tasks Analyses

The Friedman test revealed an effect of participant [$X^2_F(49) = 74.90$, $p = 0.01$]. The Spearman correlations between the questionnaires and the readouts of the behavioral tasks are shown in **Table 1**. We found one significant correlation between cognitive concerns (ASI) and Path-Choice ($r_s = 0.30$, $p < 0.05$), but this did not survive correction for multiple testing. No (uncorrected) significant correlations were found with any of the other scales from the pre- or post-experiment questionnaires. The results of the sex comparisons are listed in **Table 2** and shown in **Supplementary Figure 1**.

Discussion

In this quasi-experiment, we tested whether avoidance behavior induced by differential fear conditioning can be quantified by

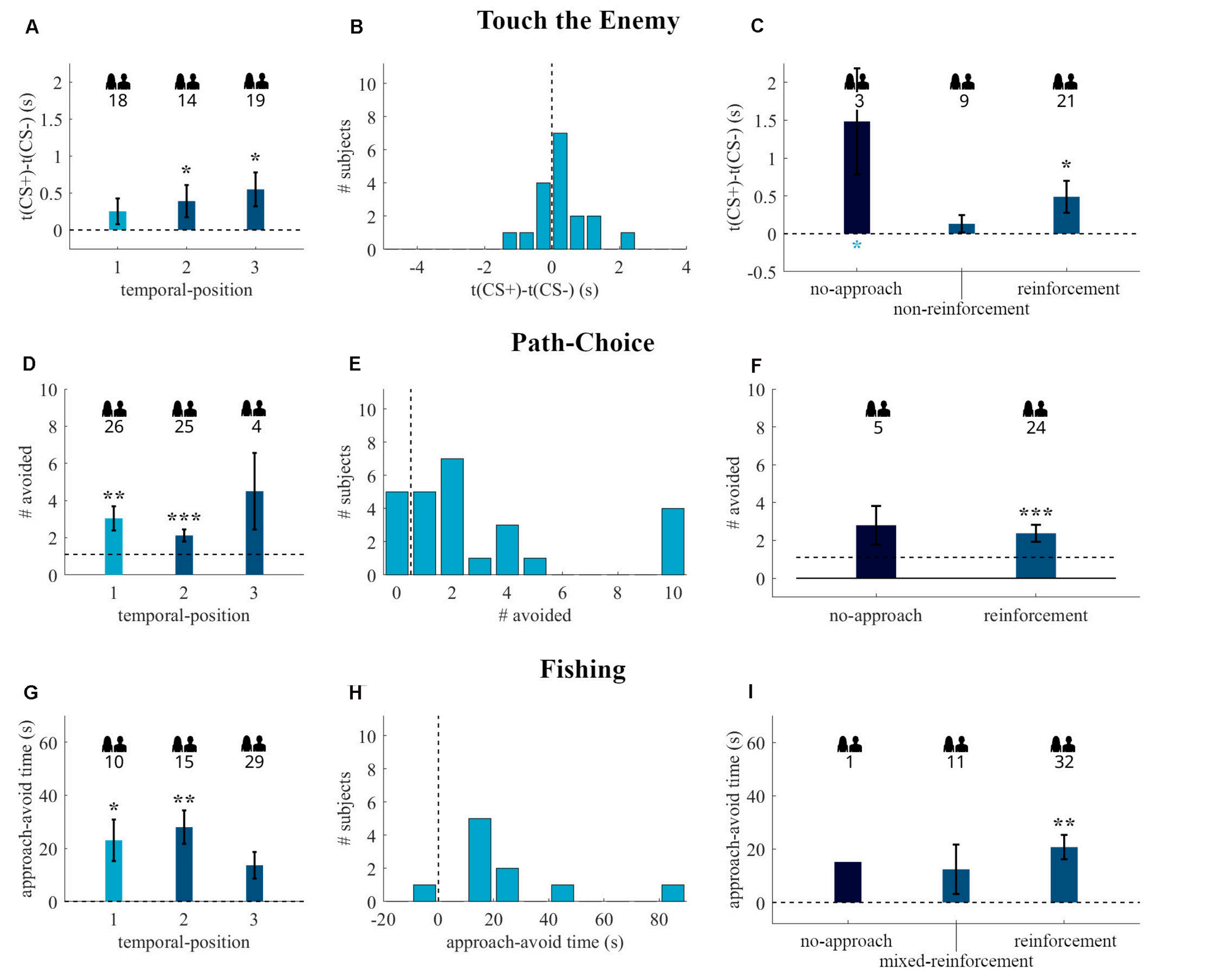

FIGURE 4 | Behavioral readouts of the Touch the Enemy **(A–C)**, Path-Choice **(D–F)**, and Fishing **(G–I)** tasks in the **quasi-experiment**. The first column **(A,D,G)** depicts the readouts (mean and standard error) of the tasks grouped by the temporal-position in the individual task sequence. The second column **(B,E,H)** shows the histograms of participants that started with the respective task after fear conditioning (temporal-position one in **A,D,G**). The third column **(C,F,I)** contains the data (mean and standard error) of participants with temporal-position two and three, regrouped by the CS+-Experience categories. The dark blue bars are the no-approach categories, which were excluded in the CS+-Experience tests. Dashed lines indicate the border between approach (lower values) and avoidance (higher values) behavior. The numbers below the people indicate the number of participants included in the respective group. Black * above bars represent (uncorrected) significance levels of one-sample tests. Blue * below bars represent significance levels of comparison to temporal-position one. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

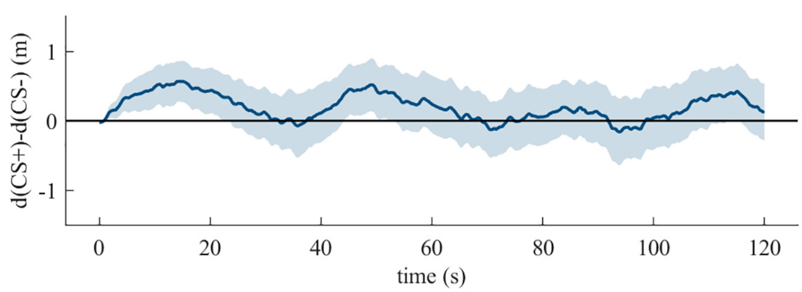

FIGURE 5 | The mean with 95% confidence interval of the difference between the distances from the participant to the CS+ and the CS- by time for the duration of the Fishing task in the **quasi-experiment**.

TABLE 1 | Spearman correlations between questionnaires and behavioral tasks in the **quasi-experiment**.

		Value		Correlation							
		M	**SD**	**Touch the Enemy**		**Path-Choice**		**Fishing**		**Rank-Sum**	
				r_s	p	r_s	p	r_s	p	r_s	p
Task	Touch the enemy	0.35	0.79								
	Path-Choice	2.54	2.45	0.16	0.27						
	Fishing	19.12	26.71	0.23	0.11	0.41	0.003				
	Rank-Sum	76.50	31.00	**0.64**	<0.001	**0.73**	<0.001	**0.73**	<0.001		
	Age	24.42	4.20	–0.20	0.17	0.22	0.12	**0.30**	0.04	0.11	0.44
Valence rating	Shock (US)	6.22	1.39	–0.03	0.86	**0.36**	0.01	0.21	0.14	0.27	0.06
	CS+	–3.10	1.75	**–0.31**	0.03	**–0.35**	0.01	**–0.38**	0.007	**–0.48**	<0.001
	CS-	3.96	1.65	0.25	0.08	0.09	0.51	0.20	0.17	0.22	0.12
	CS- minus CS+	7.06	3.01	**0.36**	0.01	0.26	0.07	**0.38**	0.007	**0.44**	0.001

Bold = $p < 0.05$.

three behavioral tasks. Moreover, we tested the influence of additional reinforcement on this avoidance behavior.

Participants subjectively learned the contingency between the CSs and the US and this was still manifest in the Recall task after the behavioral tasks. Also, there was a significant increase in heart rate during the CS+ compared to the CS-. We observed no avoidance behavior in the behavioral approach task (Touch the Enemy), if it immediately followed the Fear Conditioning task. After additional reinforcement, participants showed avoidance behavior in this task. With the behavioral forced-choice (Path-Choice) and search tasks (Fishing), we observed avoidance behavior independent of additional reinforcement. In addition, we found that the occurrence of a non-reinforced trial in a preceding task eliminated avoidance behavior in the behavioral search task.

This quasi-experiment had multiple manipulations between the runs and no randomization between groups. The idea of analyzing the effect of additional reinforcement with categories of CS+-Experience emerged during the quasi-experiment. Due to this design, one could argue that the effects are to some extent confounded by recruiting time and other factors.

To examine these possibilities, we ran a confirmatory experiment, in which we randomly assigned participants to different task-orders, with counter-balanced reinforcement/non-reinforcement to ensure that there were enough participants in the relevant CS+-Experience categories. Additionally, we used a more intense US, consisting of a 2 s female voice scream together with three consecutive electrical shocks, since avoidance effects were rather small for some tasks and correlational analyses suggested a weak correlation between CS valence and avoidance behavior.

EXPERIMENT

Materials and Methods

The procedure of the experiment was largely identical to the quasi-experiment with the following modifications:

We measured 77 participants in this experiment: 3 of them dropped out due to technical issues with Unity, 1 canceled at the very beginning due to dizziness in iVR, and 1 was removed from analysis, as he reported to hardly perceive the electrical shocks. The excluded participants were replaced with new participants until the predefined 72 participants (M = 24.2, SD = 4.4, range = 18–34, female: 40) were reached. Participants were randomly assigned to 12 equal-sized groups with 6 different task orders and whether the CS+ approach in the first task was reinforced or not. In the second and third behavioral task a CS+ approach was always reinforced. One participant walked through the table in the Path-Choice task and was excluded from analyses of that task, as well as the across tasks analyses. In the heart rate analyses, we excluded 8 participants in the Fear Conditioning task and 11 participants in the Recall task, due to missing data after technical problems with the device.

We increased the intensity of the US as the effects in the quasi-experiment were rather small and we observed a weak correlation between avoidance behavior and CS valence. The US was a 95 dB female voice scream (first 2 s of no. 276 in IADS-2, Bradley and Lang, 2007), played simultaneously with three consecutive 100 ms electrical shocks (400 and 700 ms breaks). The calibration of a single electrical shock was identical to the quasi-experiment. Participants received the combined US the first time during the Fear Conditioning task.

The Tutorial was extended by a short scream habituation after the calibration of the electrical shock: Participants were informed that beside the electrical shock they will also hear a female voice scream. They heard it once alone and rated its valence afterward on the same scale as the electrical shock. In the Fear Conditioning

TABLE 2 | Sex comparisons of the behavioral tasks with test statistic and p-values of the Mann-Whitney U-test and Cohens U3 effect sizes.

	Male (N = 22)		Female (N = 28)		Test		
	M	***SD***	***M***	***SD***	**U**	**P**	**U3**
Touch the enemy	0.3	0.8	0.4	0.8	292.0	0.764	0.55
Path-Choice	2.4	2.2	2.6	2.7	310.5	0.964	0.50
Fishing	15.3	26.9	22.1	26.7	251.0	0.272	0.73
Rank-Sum	73.3	29.1	79.0	32.7	275.5	0.532	0.64

task, we adapted the rating question for the new US to "How likely does an unpleasant stimulus occur for that object?" In the Path-Choice task, we moved the balloons next to the table in the center and introduced a pause of 2 s between finishing the trial and starting the next one. This was done to increase salience and recognition of the balloons to avoid incidental approaches of the CS+ after swapping of the CSs. In the Fishing task, the handle of the hand-net was shortened from 0.75 to 0.35 m to encourage more movement.

At the end, after the virtual reality experience, we added the iGroup Presence Questionnaire (Schubert et al., 1999) to the surveys to improve comparability to other studies.

Results

Mean electrical shock current was 3.0 mA (*SD* = 1.1 mA). Participants rated it after the experiment as unpleasant (*M* = 7.2, *SD* = 1.3, scale = 1–10). The scream alone was perceived as less unpleasant (*M* = 3.7, *SD* = 2.1, scale = 1–10), while the combination of scream and electrical shocks were rated with a mean of 6.7 (*SD* = 1.5, scale = 1–10). We further analyzed potential differences in habituation according to US intensity (see **Supplementary Material**). As shown in **Figure 6**, participants reported high presence in the Presence Questionnaire 3 (*M* ± *SD*): involvement, 5.0 ± 0.7; sensory fidelity, 4.6 ± 1.0; adaptation immersion, 5.8 ± 0.5; interface quality, 2.5 ± 0.9. In the iGroup Presence Questionnaire they also reported high presence: general presence, 4.2 ± 1.3; spatial presence, 4.5 ± 0.9; involvement, 3.9 ± 1.2; experienced realism, 2.5 ± 1.1. Moreover, they reported only slight side effects in the Simulator Sickness Questionnaire: total score, 19.8 ± 21.0; nausea, 19.9 ± 20.7; oculomotor symptoms, 12.4 ± 13.9; disorientation, 21.8 ± 31.2.

Fear Conditioning and Recall

The analyses of the shock expectancy ratings during the Fear Conditioning (**Figure 7A**) and Recall (**Figure 7B**) tasks revealed a significant stimulus effect [$F(1, 71) = 897.2$, $p < 0.001$, $\eta_p^2 = 0.93$, $\eta_G^2 = 0.73$], a time effect [$F(2, 142) = 5.75$, $p = 0.004$, $\eta_p^2 = 0.07$, $\eta_G^2 = 0.03$], and a stimulus × time interaction [$F(2, 142) = 421.4$, $p < 0.001$, $\eta_p^2 = 0.86$, $\eta_G^2 = 0.61$] during fear conditioning and a stimulus effect [$F(1, 71) = 591.0$, $p < 0.001$, $\eta_p^2 = 0.89$, $\eta_G^2 = 0.68$], a time effect [$F(1, 71) = 241.0$, $p < 0.001$, $\eta_p^2 = 0.77$, $\eta_G^2 = 0.43$], and a stimulus × time interaction [$F(1, 71) = 199.1$, $p < 0.001$, $\eta_p^2 = 0.74$, $\eta_G^2 = 0.39$] during recall.

The RR-changes during the Fear Conditioning and Recall tasks are shown in **Figures 7C,D**, respectively. The analyses revealed a stimulus effect [$F(1, 63) = 9.60$, $p = 0.003$, $\eta_p^2 = 0.13$, $\eta_G^2 = 0.01$] and trial effect [$F(9, 567) = 9.58$, $p < 0.001$, $\eta_p^2 = 0.13$, $\eta_G^2 = 0.05$], but no stimulus × trial interaction [$F(9, 567) = 1.56$, $p = 0.124$, $\eta_p^2 = 0.02$, $\eta_G^2 = 0.01$] during fear conditioning. None of the factors stimulus [$F(1, 60) = 1.76$, $p = 0.19$, $\eta_p^2 = 0.03$, $\eta_G^2 = 0.00$] and trial [$F(3, 180) = 1.97$, $p = 0.12$, $\eta_p^2 = 0.03$, $\eta_G^2 = 0.01$] or the interaction stimulus × trial [$F(3, 180) = 2.40$, $p = 0.07$, $\eta_p^2 = 0.04$, $\eta_G^2 = 0.02$] were significant during recall.

Touch the Enemy

The ANOVA revealed an effect of temporal-position [$F(2, 69) = 4.20$, $p = 0.019$, $\eta^2 = 0.11$] and, as depicted in **Figure 8A**, the time to touch difference increased with rising temporal-position. The t-tests on the single temporal-positions revealed no significant avoidance for temporal-position one [$t(23) = -0.27$, $p = 0.61$, $g_1 = -0.06$, see **Figure 8B**] and two [$t(23) = 1.51$, $p = 0.07$, $g_1 = 0.31$], but if this was the last task, avoidance behavior could be observed [$t(23) = 2.82$, $p = 0.005$, $g_1 = 0.58$]. The ANOVA revealed an effect of CS+-Experience [$F(3, 61) = 3.76$, $p = 0.02$, $\eta^2 = 0.16$, see **Figure 8C**]. The t-tests on the single CS+-Experience categories revealed no time to touch difference significantly higher than zero for non-reinforcement [$t(8) = -0.11$, $p = 0.54$, $g_1 = -0.04$] and mixed-reinforcement [$t(7) = -1.38$, $p = 0.89$, $g_1 = -0.49$] but we observed significant avoidance behavior in the categories reinforcement [$t(23) = 2.92$, $p = 0.004$, $g_1 = 0.60$] and no-approach [$t(6) = 2.53$, $p = 0.02$, $g_1 = 0.96$]. The independent *t*-tests between temporal-position one and the CS+-Experience categories revealed no increase for non-reinforcement [$t(31) = -0.10$, $p = 0.92$, $\Delta = -0.04$] and mixed-reinforcement [$t(30) = 0.39$, $p = 0.70$, $\Delta = 0.14$], however, the comparisons revealed an significant increase in the time to touch difference for no-approach [$t(29) = -2.60$, $p = 0.01$, $\Delta = -1.12$], and reinforcement [$t(46) = -2.58$, $p = 0.01$, $\Delta = -0.94$].

Path-Choice

Analyses of Path-Choice revealed no effect of temporal-position [$X^2(2, N = 71) = 4.49$, $p = 0.11$]. As shown in **Figure 8D**, there was no avoidance behavior in temporal-position one ($p = 0.20$, $N = 23$, 14 avoiders), but there was an effect, when the task was in second ($p = 0.01$, $N = 24$, 18 avoiders) or third place ($p < 0.001$, $N = 24$, 22 avoiders). Fourteen out of 23 participants with Path-Choice as first behavioral task avoided the CS+ at least once (see **Figure 8E**). The analysis by CS+-Experience (see **Figure 8F**) revealed an effect of categories [$X^2(3, N = 69) = 13.42$, $p = 0.004$]. The binomial tests on single categories revealed an effect for reinforcement ($p < 0.001$, $N = 25$, 23 avoiders) and mixed-reinforcement ($p = 0.02$, $N = 9$, 8 avoiders), but we did not observe significant avoidance behavior for non-reinforcement ($p = 0.39$, $N = 12$, 7 avoiders) and no-approach ($p = 0.25$, $N = 2$,

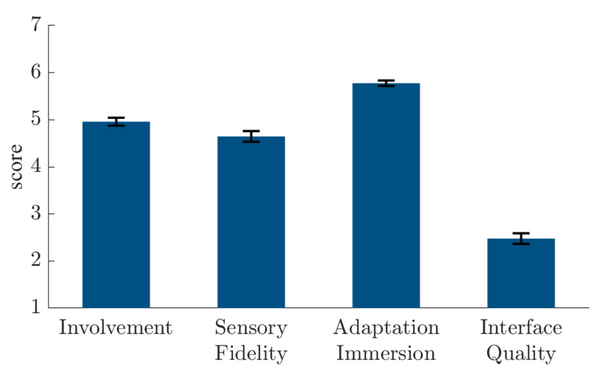

FIGURE 6 | Presence Questionnaire 3 (Witmer et al., 2005) scores in the **experiment**.

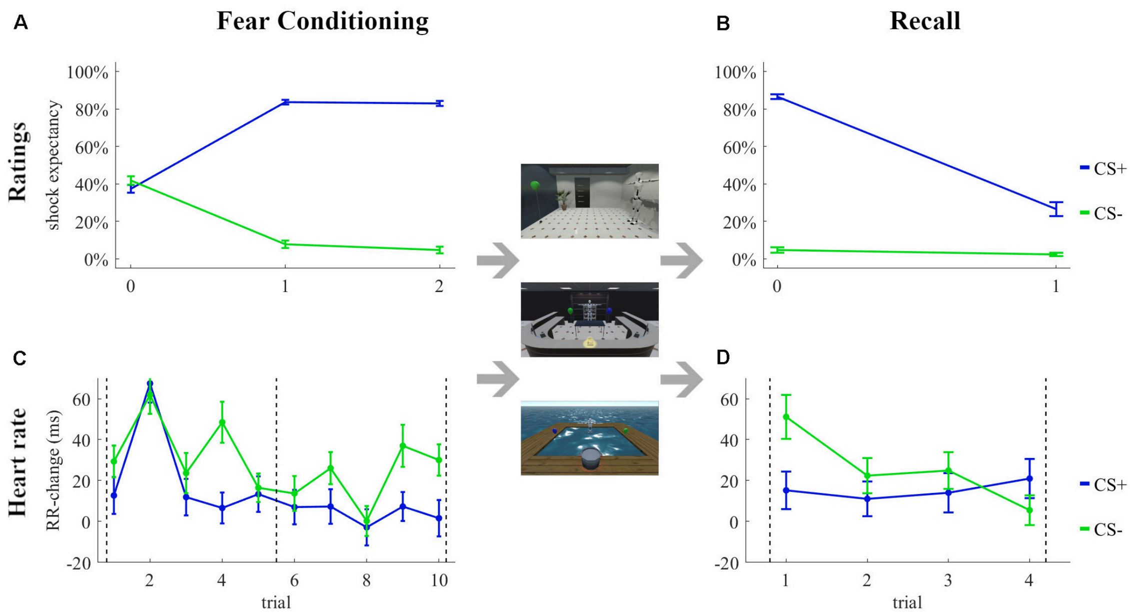

FIGURE 7 | Subjective ratings **(A,B)** and changes in heart rate **(C,D)** during the Fear Conditioning **(A,C)** and Recall **(B,D)** tasks in the **experiment**. Rating 0 was the first subjective rating before the first trial. Dashed lines in **(C,D)** indicate the subjective ratings.

2 avoiders). The comparison of the temporal-position one to the CS+-Experience categories revealed no significant difference for no-approach [$U(n_1 = 23, n_2 = 2) = 16$, $p = 0.54$, $U3 = 0.74$], non-reinforcement [$U(n_1 = 23, n_2 = 12) = 149$, $p = 0.14$, $U3 = 0.41$], mixed-reinforcement [$U(n_1 = 23, n_2 = 9) = 84.5$, $p = 0.43$, $U3 = 0.50$], and reinforcement [$U(n_1 = 23, n_2 = 25) = 204$, $p = 0.08$, $U3 = 0.65$].

Fishing

The Kruskal-Wallis test revealed no effect of temporal-position [$X^2(2, N = 72) = 1.85$, $p = 0.40$]. As shown in **Figure 8G**, there was avoidance behavior regardless of whether this task was in first ($p < 0.001$, $N = 24$, 21 avoiders), second ($p < 0.001$, $N = 24$, 21 avoiders), or third ($p < 0.001$, $N = 24$, 20 avoiders) place. **Figure 8H** shows that 21 out of 24 participants with Fishing as first behavioral task avoided the CS+, whereas the other participants approached the CS+ at the beginning. The analysis on the CS+-Experience showed no group effect [$X^2(3, N = 68) = 5.97$, $p = 0.11$, see **Figure 8I**]. The binomial tests revealed significant avoidance behavior for the category reinforcement ($p < 0.001$, $N = 24$, 23 avoiders), but not for no-approach ($p = 0.06$, $N = 4$, 4 avoiders), non-reinforcement ($p = 0.25$, $N = 9$, 6 avoiders), and mixed-reinforcement ($p = 0.11$, $N = 11$, 8 avoiders). The temporally dynamic analysis again showed that avoidance behavior was confined to the first twenty seconds (see **Figure 9**).

Across Tasks Analyses

The Friedman test revealed an effect of participant [$X^2(70) = 101.07$, $p < 0.01$]. The Spearman correlations between the questionnaires and the readouts of the behavioral tasks are shown in **Table 3**. We found nominally significant correlations between nausea (SSQ) and Path-Choice ($r_s = 0.26$, $p < 0.05$), between sensory fidelity (PQ3) and Path-Choice ($r_s = 0.30$, $p < 0.05$), between interface quality (PQ3) and Fishing ($r_s = 0.26$, $p < 0.05$), and between somatic concerns (ASI) and Fishing ($r_s = 0.26$, $p < 0.05$), but none survived correction for multiple testing. No (uncorrected) significant correlations were found with any of the other scales from the pre- or post-experiment questionnaires. The results of the sex comparisons are listed in **Table 4** and shown in **Supplementary Figure 4**.

Discussion

In the confirmatory experiment, we tested the effect of differential fear conditioning with a more intense US on avoidance behavior in the same three tasks. Moreover, we manipulated whether a CS+ approach was reinforced in the first task after the Fear Conditioning task and tested the effect of this additional reinforcement on avoidance behavior in subsequent tasks. The results of the subjective ratings and heart rate analyses again demonstrated that participants learned the CS-US contingency and showed a physiological fear response to the CS+. In our behavioral approach task (Touch the Enemy), we observed avoidance behavior only in the case of additional reinforcement (without any non-reinforcement) in a preceding task, but not if it followed right after the Fear Conditioning task. Similarly, in the behavioral forced-choice task (Path-Choice), we also observed avoidance behavior only in case of an additional reinforcement in a preceding task, but not if it followed right after the Fear Conditioning task. In the behavioral search task (Fishing), we observed avoidance behavior in both cases, independent of

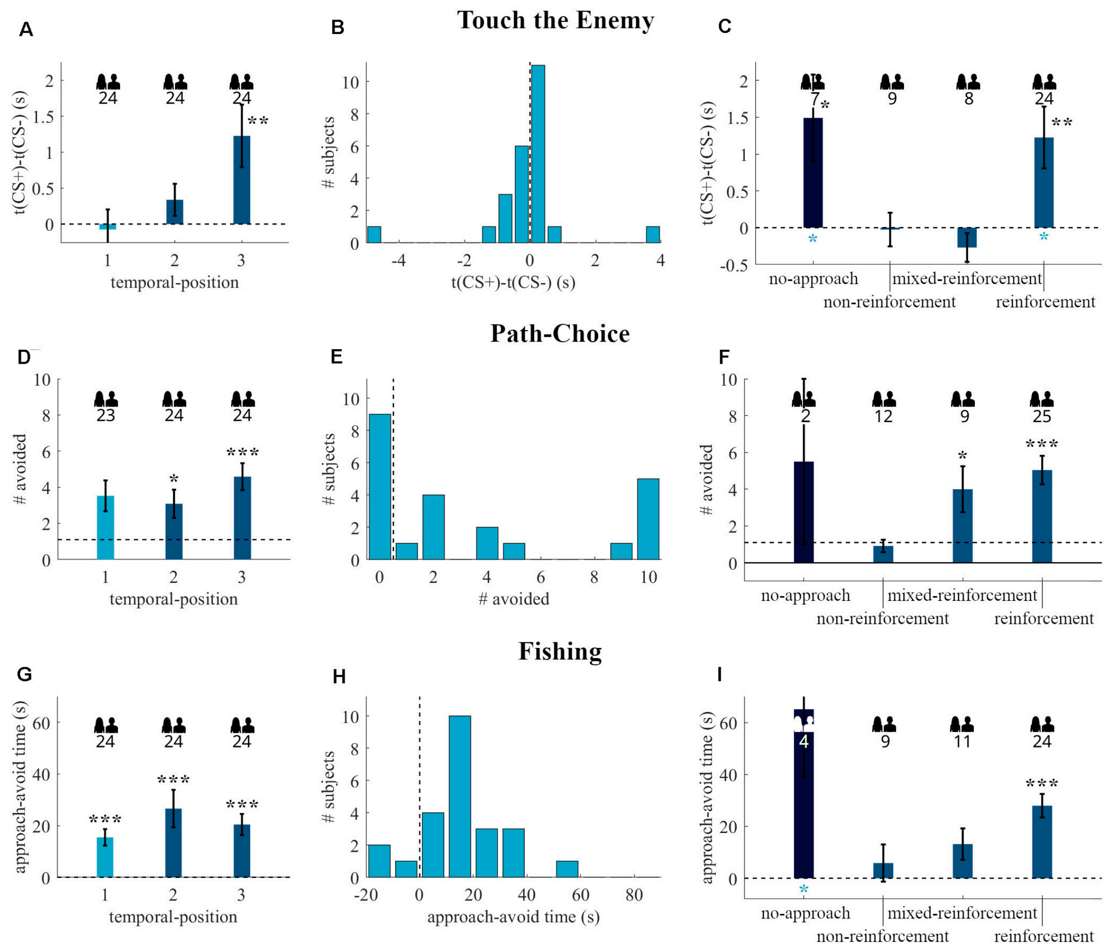

FIGURE 8 | Behavioral readouts of the Touch the Enemy **(A–C)**, Path-Choice **(D–F)**, and Fishing **(G–I)** tasks in the **experiment**. The first column **(A,D,G)** depicts the readouts (mean and standard error) of the tasks grouped by the temporal-position in the individual task sequence. The second column **(B,E,H)** shows the histograms of participants that started with the respective task after fear conditioning (temporal-position one in **A,D,G**). The third column **(C,F,I)** contains the data (mean and standard error) of participants with temporal-position two and three, regrouped by the CS+-Experience categories. The dark blue bars are the no-approach categories, which were excluded in the CS+-Experience tests. The standard error of group no-approach in **(I)** is 26.3 s, and the error-bar extends to 92.6 s. Dashed lines indicate the border between approach (lower values) and avoidance (higher values) behavior. The numbers below the people indicate the number of participants included in the respective group. Black * above bars represent (uncorrected) significance levels of one-sample tests. Blue * below bars represent significance levels of comparison to temporal-position one. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

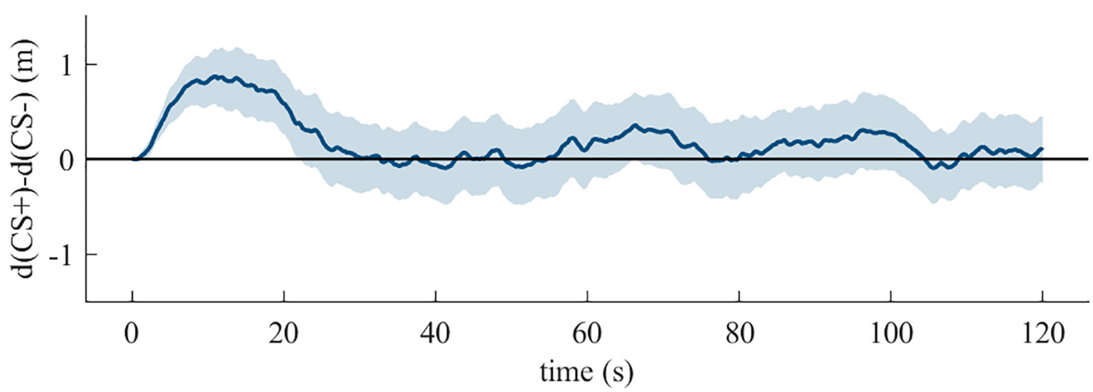

FIGURE 9 | The mean with 95% confidence interval of the difference between the distances from the participant to the CS+ and the CS- by time for the duration of the Fishing task in the **experiment**.

TABLE 3 | Spearman correlations between questionnaires and behavioral tasks in the **experiment**.

		Value		Correlation							
		M	SD	Touch the enemy		Path-Choice		Fishing		Rank-Sum	
				r_s	*p*	r_s	*p*	r_s	*p*	r_s	*p*
Task	Touch the enemy	0.51	1.67								
	Path-Choice	3.73	3.86	0.17	0.15						
	Fishing	21.04	25.40	**0.24**	0.04	**0.25**	0.04				
	Rank-Sum	108.00	42.61	**0.67**	<0.001	**0.67**	<0.001	**0.72**	<0.001		
	Age	24.25	4.37	0.15	0.21	**0.31**	0.008	0.04	0.76	0.22	0.07
Valence rating	Shock	7.21	1.32	0.09	0.48	0.21	0.07	0.23	0.05	**0.27**	0.02
	Scream	3.68	2.06	−0.03	0.80	0.19	0.12	0.15	0.22	0.13	0.29
	Combined (US)	6.72	1.54	0.18	0.14	**0.25**	0.04	**0.34**	0.004	**0.38**	0.001
	CS+	−3.76	1.25	−0.04	0.72	**−0.27**	0.02	−0.08	0.50	−0.21	0.07
	CS-	3.62	1.69	0.02	0.85	−0.18	0.14	−0.11	0.38	−0.11	0.38
	CS- minus CS+	7.38	2.07	0.07	0.57	0.02	0.90	−0.03	0.82	0.06	0.63

Bold = $p < 0.05$.

further reinforcement. However, if there was a CS+ approach without reinforcement in any preceding task, avoidance behavior was also no longer present in this task.

GENERAL DISCUSSION

In the quasi-experiment we performed four runs, analyzed them together to explore initial effects, and tested the robustness of these effects in a subsequent confirmatory experiment. The results of the second experiment provided a replication for the effects of our behavioral approach task and behavioral search task, however for the behavioral forced-choice task, the effects did not replicate to the same extent. In the confirmatory experiment, we used a more intense US to increase avoidance behavior, as analyses in the quasi-experiment showed correlations between stimulus valence and avoidance behavior. However, stimulus valence and avoidance behavior were only marginally increased in the confirmatory experiment, indicating a weaker influence of US intensity than assumed and other factors might be more important, which will be discussed below.

We compared behavioral tasks with varying instructions, degrees of freedom, and high or low task related relevance of the stimuli on the sensitivity of the tasks to detect experimentally induced avoidance behavior. The behavioral search task had the highest degrees of freedom, a gaming element ("catching a fish") and no task relevance of the CSs. Almost all participants avoided the CS+ initially, even in the case of no additional reinforcement when it followed right after the Fear Conditioning task. While they were fishing, all participants moved to the CS- side at first and remained there, on average for 20 s. These findings show that this task is sensitive for avoidance behavior after fear conditioning in healthy human participants. Our behavioral approach task had the lowest degrees of freedom and the CSs were relevant for the task, as participants were instructed to touch them. This task did not result in avoidance behavior directly after the Fear Conditioning task. Instead, we only observed avoidance behavior after additional reinforcement in previous scenarios, pointing toward its necessity. The results from the behavioral forced-choice task suggest that this task falls in between the other two. Interestingly, as participants had to pass the CSs in this task, the task relevance of the CSs was higher than in the search task but lower than in the approach task. Furthermore, in the quasi-experiment the stimuli were placed outside the paths, but in the experiment, they were placed in such a manner that participants had to walk around them. In this way the task relevance of the CSs was increased, which might explain the absence of avoidance behavior after fear conditioning in the experiment. We speculate that the lower the task relevance of the CSs, the more likely one observes avoidance behavior in that task. Other potential factors influencing the sensitivity of a task to detect avoidance behavior could be participants' degree of freedom, gamification or the cover story. However, it is open whether these factors have a direct effect on sensitivity or whether the effects are mediated by the task relevance of the stimuli.

This leads us to speculate that the more relevant the CSs are to the task, the more "cognitive" the avoidance behavior. In an unstructured *post hoc* interview, in which we asked participants why they behaved as they did, some participants reported that uncertainty in shock expectancy led to mistrust of the experimental procedure ("Now they probably changed the

TABLE 4 | Sex comparisons of the behavioral tasks with test statistic and *p*-values of the Mann-Whitney-U test and Cohens U3 effect sizes.

	Male (N = 31)		Female (N = 40)		Test		
	M	*SD*	*M*	*SD*	*U*	*p*	U3
Touch the enemy	0.3	0.9	0.7	2.1	621.0	0.993	0.35
Path-Choice	2.2	2.9	4.9	4.1	382.5**	0.004	0.77
Fishing	20.1	26.2	21.8	25.0	613.5	0.943	0.48
Rank-Sum	100.2	41.6	114.1	42.9	498.0	0.159	0.68

***$p < 0.01$.*

contingencies.") and testing behavior, resulting in an approach of the CS+. Such cognitions can be instilled by interpretations of the instructions and can lead to testing behavior of individually developed hypotheses. We hypothesize that differences in cognitions explain a high proportion of the variance in individual differences in behavior. However, it is difficult to objectively and reliably measure cognitions directly, without affecting them; nevertheless, the individual creation and testing of hypotheses should be considered in future research, possibly initially with more qualitative approaches.

Avoidance behavior is often weighed against other behavioral alternatives with competing motivations. These comprise the situational evaluation of likelihoods, including information of the efficacy of responses and the cost of avoidance (Sheynin et al., 2015; Servatius, 2016). The presented behavioral tasks differ in the number of possible behaviors, the efficacy of participants' responses in avoiding the US, as well as the cost of avoidance. Thus, various forms of avoidance behavior across the tasks can be expected. In line with that, the cross-correlations among the behavioral tasks showed only one weak correlation, between the behavioral search and forced-choice tasks, in both experiments. This relationship was also evident in the pattern of the CS+-Experience of the tasks: In all tasks, we observed avoidance behavior in the reinforcement category but not in the non-reinforcement category. However, in the behavioral search and forced-choice tasks, we also observed avoidance behavior in the mixed-reinforcement category, which was not the case for our behavioral approach task. These findings suggest that the observed avoidance behavior might be rather task-specific, and the different CS+-Experience patterns indicate that avoidance in different tasks might be based on different learning mechanisms. This is in line with the Principles of Avoidance Learning (Krypotos et al., 2015): According to this theory, Pavlovian conditioning is sufficient for action tendencies and the necessity of instrumental conditioning is depending on the type of the behavioral response.

Another important question is whether reinforcement during the behavioral tasks can be interpreted as instrumental conditioning. Existing theories of avoidance learning (Krypotos et al., 2015) differ in the role of instrumental conditioning and the assumed reinforcer, but most assume positive reinforcement of the avoidance behavior. In our study, approach and avoidance behavior differed across the tasks, so it could be argued that no specific behavior was reinforced or at least that it was too generic. The effects we observed could have been due to additional reinforcement functioning as generalization of CS-US contingencies across contexts and scenes. In our opinion, the most likely interpretation is that the reinforcement strengthened the CS-US contingencies. Even though we used a high reinforcement rate during fear conditioning and asked for the probability of receiving a shock, the ratings could have reflected only the past reinforcement rate instead of a future expectation with included uncertainty. We speculate that, in addition to the only slight increase in the reinforcement rate, the uncertainty was greatly reduced, and thus the CS-US contingency was strengthened. This impression was supported by many comments in the *post hoc* interview regarding the uncertainty (e.g., "It could have been that there was no shock", "Was not sure if there would be a shock.").

The manipulation of reinforcement during the behavioral tasks also enabled us to investigate the effect of non-reinforcement trials on behavior in subsequent tasks. These non-reinforcement trials can be interpreted as an extinction phase. In line with literature on extinction learning (Milad and Quirk, 2012) and exposure therapy (Foa and Kozak, 1986; Craske et al., 2014), we observed that non-reinforcement trials in one task extinguished avoidance behavior in the subsequent task, independent of the type of the tasks. However, this acquisition of avoidance might be an adaptive mechanism, whereas pathological anxiety could be better modeled by the persistence of avoidance behavior after the threat is gone. Our results indicate that the tasks can also be used to investigate this pathological avoidance. To do so, future work could add a new extinction task after the Fear Conditioning task or compare avoidance behavior after non-reinforcement in the behavioral search task to avoidance behavior after non-reinforcement in the approach task, examining the effects of explicit vs. implicit approach.

Beside the inter-task differences, we also observed robust within-task inter-individual differences. The participants were distributed on a wide range of avoidance intensities in each task, even in the behavioral search task, in which most participants avoided the CS+ in the beginning. Such dimensional behavioral expressions of avoidance might be useful in translating basic science to psychopathology (Servatius, 2016; Krypotos et al., 2018). Interestingly, the distribution appeared bimodal in the forced-choice task, indicating subtypes of behavior rather than a continuous dimension. Furthermore, we found some consistent individual differences across tasks, indicating that some participants show high avoidance behavior in all tasks and some participants show low avoidance behavior in all tasks, even though the correlations between the tasks were weak at best. This raises the question whether these differences are driven by trait factors. Pittig et al. (2020) listed trait anxiety, intolerance of uncertainty, anxiety sensitivity, neuroticism, and age as possible moderators of avoidance. However, our analyses did not show any robust correlations, which are present in both experiments, between avoidance behaviors and traits assessed by subjective questionnaires. Regarding sex differences, Sheynin et al. (2014) and Pittig et al. (2020) reported enhanced avoidance in female compared to male participants. In line with that, we found increased avoidance in female participants in the behavioral forced-choice task. However, we observed this difference only in that task, and even this effect was only present in the confirmatory experiment, but not in the quasi-experiment.

It remains therefore an open question, whether traits and sex explain much variance in individual differences in avoidance behavior, and how this phenomenon can be further explained. One possible direction for this question would be the comparison of healthy controls with patients. In our sample, we included only healthy participants, which limited the variance in the questionnaires. Extending the study protocol to patients with anxiety disorders would increase variance, and could also increase avoidance behavior, which might help explain individual differences.

The changing contexts might bring up the question whether they have led to a reduction of avoidance behavior, as participants might not automatically generalize from one scene to the next in iVR. We picked this approach as we were interested in cued fear conditioning. In animal research, this usually involves different contexts for different experimental phases to minimize contextual effects and maximize effects from CS-US pairing (Maren et al., 2013; Lonsdorf et al., 2017). In humans, this has been done only sometimes, due to methodological difficulties. It is plausible that procedures using the same context, as done in a monitor-based virtual environment study before (Greville et al., 2014), would have led to more robust avoidance behavior. In our study, however, it could have led to some difficulties in finding a one-size-fits-all solution for the various tasks and to transfer effects across scenes. For instance, during the search task, participants could have avoided the position where the CS+ was placed in the preceding task. One of the strengths of iVR is that context has become a factor that can more easily be experimentally manipulated, which opens the field for new research questions.

A limitation of the current study relates to CS+-Experience. According to its definition, it is task specific. This means, that the CS+-Experience for one behavioral task is based on participants' behavior in the two other tasks. For instance, reinforcement before our behavioral approach task must occur in the behavioral search or forced-choice tasks, whereas reinforcement for the behavioral search task must occur in our behavioral approach or forced-choice tasks. Within our definition of CS+-Experience, the reinforcements in the different behavioral tasks are treated the same, but there could be a difference between the reinforcement when touching the CS+ as in our behavioral approach task, and the reinforcement when passing by the CS+ as in the behavioral search or forced-choice tasks. Nevertheless, if we compare two behavioral tasks, the context of their CS+-Experience has an overlap of 50%, as the third task is the same for both. Another limitation of what we defined as CS+-Experience is that it is based on participants' behavior, which they could freely choose. A participant had to have approached the CS+ to be able to undergo non-reinforcement and/or reinforcement, and some did not. As less than 10% of participants were "full avoiders," we can expect the effect of this confound on our results to be low. To overcome these difficulties, future research should consider inserting an instrumental conditioning task with no degrees of freedom after the Fear Conditioning task, but before the behavioral tasks. Another limitation relates to the motion of the CSs. During the Fear Conditioning task, the CSs were floating toward participants or into the air. However, in the behavioral search task, they swayed slightly in the wind and in our behavioral approach and forced-choice task, they did not move. It is possible that motion is a salient element of the stimuli, although the difference between a CS floating toward participants vs. minimal stationary swaying appears rather large.

In our study, we developed a new paradigm in iVR to experimentally induce and assess avoidance behavior. Participants were placed in the virtual scenes, could freely look around, saw a representation of their body, and navigated by naturalistic movements. This resulted in a very high presence with hardly any side effects, as well as naturalistic body movements and real-life behavior of participants within these artificial environments. The tasks of touching, choosing, and searching are common real-life behaviors. Therefore, the ecological validity of iVR appears high. Another advantage of this approach is that participants are confronted with the CS instead of the US, which might model a comparable process in anxiety disorders (Krypotos et al., 2015).

CONCLUSION

To conclude, we observed avoidance behavior in all three tasks, probing different types of avoidance behavior. The behavioral approach and forced-choice tasks were sensitive to "strong" avoidance behavior after additional reinforcement, whereas the most sensitive task to detect avoidance behavior after fear conditioning was our behavioral search task, with low task relevance of the CSs, the highest degrees of freedom, and distraction by gamification elements.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Faculty of Medicine at Ludwig Maximilian University of Munich. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FB and VS designed the study. FB developed and implemented the tasks, recruited the participants, acquired and analyzed the data. FB and VS interpreted the data. FB wrote the manuscript under supervision of VS. All authors read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2020.569899/full#supplementary-material

Supplementary Video 1 | Video of the Touch the Enemy task.

Supplementary Video 2 | Video of the Path-Choice task.

Supplementary Video 3 | Video of the Fishing task.

Supplementary Data Sheet 1 | Supplementary tables and figures.

Supplementary Data Sheet 2 | Underlying data of the **quasi-experiment**.

Supplementary Data Sheet 3 | Underlying data of the **experiment**.

Supplementary Data Sheet 4 | Unity package containing the virtual scenes.

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3. Paper II

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Facing Your Fear in Immersive Virtual Reality: Avoidance Behavior in Specific Phobia

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Specific phobias are the most common anxiety disorder and are characterized by avoidance behavior. Avoidance behavior impacts daily function and is proposed to impair extinction learning. However, despite its prevalence, its objective assessment remains a challenge. To this end, we developed a fully automated experimental procedure using immersive virtual reality. The procedure contained a behavioral search, forced-choice, and an approach task with varying degrees of freedom and task relevance of the stimuli. In this study, we examined the sensitivity and feasibility of these tasks to assess avoidance behavior in patients with specific phobia. We adapted the tasks by replacing the originally conditioned stimuli with a spider and a neutral animal and investigated 31 female participants composed of 15 spider-phobic and 16 non-phobic participants. As the non-phobics were quite heterogeneous in terms of their Fear of Spiders Questionnaire (FSQ) scores, we subdivided them into six "fearfuls" that had elevated FSQ scores, and 10 "non-fearfuls" that had no fear of spiders. The phobics successfully managed to complete the procedure and showed consistent avoidance behavior across all behavioral tasks. Compared to the non-fearfuls, which did not show any avoidance behavior at all, the phobics looked at the spider much more often and clearly directed their body toward it in the search task. In the approach task, they hesitated most when they were close to the spider, and their difficulty to touch the spider was reflected in a strong increase in right hand acceleration changes. The fearfuls showed avoidance behavior depending on the tasks: strongest in the search task and weakest in the approach task. Additionally, we identified subjective valence ratings of the spider as the main influence on both objective avoidance behavior and subjective well-being after exposure, mediating the effect of the FSQ. In summary, the behavioral tasks are well suited to assess avoidance behavior in phobic participants and provide detailed insights into the process of avoidance.

Keywords: anxiety disorders, specific phobia, avoidance behavior, immersive, virtual reality, arachnophobia, spider phobia, exposure

INTRODUCTION

Anxiety disorders are the most common mental disorders with 14% of the population being affected by an anxiety disorder (Wittchen et al., 2011). Pathological fear or anxiety differs from normal feelings of arousal or nervousness in that the levels of fear and anxiety are out of proportion to the actual danger (American Psychiatric Association, 2013). With a prevalence of 6.4%, specific phobia is the most common anxiety disorder (Wittchen et al., 2011).

Avoidance behavior is a key symptom of anxiety disorders. Individuals with specific phobia intentionally behave in ways that prevent or minimize contact with the phobic object and avoid situations in which the phobic object might appear (American Psychiatric Association, 2013). This avoidance behavior leads to significant distress and impairment in important areas of functioning, such as in their social or occupational environments. In addition, avoidance behavior prevents fear extinction, thus maintaining the fear (Lovibond et al., 2009). Despite its importance, the clinical and scientific investigation of avoidance behavior remains a challenge. In clinical contexts, avoidance behavior is usually assessed by self-monitoring and self-report (Antony et al., 2002; Grös and Antony, 2006), such as with the Acceptance and Action Questionnaire (Hayes et al., 2004; Bond et al., 2011). In anxiety research, avoidance behavior is typically operationalized as a decision captured by pressing buttons (Pittig et al., 2014; Sheynin et al., 2014; Krypotos et al., 2018; Luo et al., 2018) or moving a joystick (Grillon et al., 2006). Another way to assess avoidance behavior in specific phobia, used in both contexts, is the Behavioral Avoidance Test. In this task, subjects are confronted by the feared object and asked to approach it as close as possible (Antony et al., 2002; Grös and Antony, 2006). Although the test yields valid and reliable quantification of avoidance behavior, it is very disturbing for the patients and the provision and implementation is costly, as the feared objects, often animals, must be present and cared for. Therefore, an interesting alternative to the presentation of real feared objects is the presentation of virtual objects in virtual reality (VR).

In early VR-based approaches, artificial scenarios were presented to participants on a screen in front of them, and they navigated them with a joystick or by pressing buttons. In immersive VR (iVR), participants wear VR goggles with a screen for each eye that provides a stereoscopic first-person view of the artificial environment. The position and rotation of the goggles are tracked and reflected in the artificial environment. Thus, participants get a three-dimensional all-round view and navigate using head movements as they would in their natural environment. The main advantages of iVR are the full controllability of the environment, the very high standardization, the ease of switching between different environments and the possibility to record all relevant data for later analysis. To use these advantages in the Behavioral Avoidance Test, Mühlberger et al. (2008) developed a Virtual Reality Behavioral Avoidance Test for arachnophobia. In this test, female spider-phobic participants sat on a chair wearing VR goggles and used a joystick to move as close as possible to a spider in the virtual room. They showed that higher levels of fear of spiders were associated with less approach behavior (Mühlberger et al., 2008).

Immersive virtual reality was used to investigate avoidance behavior in spider-fearful participants by Rinck et al. (2010). Their participants wore VR goggles and navigated by walking around freely. The task was to search for certain paintings within a virtual museum with several rooms, some of which contained spiders. They showed that spider-fearful participants had an increase in state anxiety, spent more time looking at spiders, and were more engaged in spontaneous avoidance behavior toward spiders. In our previous work (Binder and Spoormaker, 2020), we used the iVR approach to examine if we could objectively quantify avoidance behavior after Pavlovian fear conditioning. In our setup, the healthy participants wore VR goggles and a full-body motion tracking system that provided a virtual representation of participant's body in the artificial environment. Participants used their naturally controlled body representation to interact in VR. We developed a behavioral search, a forced-choice, and an approach task to cover a broader range of human behavior and to examine the consistency of avoidance behavior. The tasks differ in degrees of freedom, gamification level, and task relevance of the conditioned stimuli. Higher degrees of freedom lead to more ecological validity, but also increase complexity and analytical flexibility. Gamification was used to get participants to move while distracting them and allowing the capture of more implicit behavior. The task relevance of the conditioned stimuli is usually high in fear conditioning paradigms, but low task relevance can be beneficial in detecting relationships between task performance and trait anxiety (Dodd et al., 2017) or phobic fear (Okon-Singer et al., 2011). We observed that in healthy controls, the behavioral search task with low task relevance of the conditioned stimuli, the highest degrees of freedom, and distraction by gamification elements, was the most sensitive to detect avoidance behavior for the conditioned stimuli. The forced-choice task showed a bimodal distribution with some participants consistently avoiding the conditioned stimuli, and others displaying no initial avoidance behavior. However, the approach task was only sensitive to "strong" avoidance behavior after additional reinforcement.

The goal of this study was to examine the sensitivity and feasibility of these tasks to assess avoidance behavior in patients with specific phobia. This would allow a standardized quantification of avoidance behavior in patients and the online assessment of avoidance behavior during potentially automated therapeutic sessions. Furthermore, we aimed to characterize avoidance behavior in more detail, as our setup allows the continuous tracking of head, limb and body movements in VR and heart rate, as well as pupil size and gaze behavior by incorporation of an integrated eye-tracking system. Heart rate is regulated by the autonomic nervous system and has been proposed to reflect physiological arousal (Berntson et al., 2016), one of the dimensions on which emotions are commonly described (Lang, 1985). Pupil size has been associated with a range of cognitive and affective processes, from cognitive effort to uncertainty and memory (Mathôt, 2018). In threat-related contexts, pupil dilation appears to reflect the salience of stimuli and increases with increasing arousal of stimuli in a valence-independent manner (Hess and Polt, 1960; Aston-Jones and Cohen, 2005; Bradley et al., 2008). Gaze behavior reflects attentional processes that have been shown to be altered in patients with spider phobia (Abado et al., 2020). We focused on spider phobia in our experiments, as the phobic object is well defined, and the prevalence is high. Around one third of the population has a strong dislike of spiders (Davey, 1991; Muris et al., 1997) with females being more affected than males, at rates of 5:1 (Fredrikson et al., 1996). To contrast with the spider, we used a turtle as a neutral control stimulus to detect response differences to these stimuli. With this setup, we could evaluate which tasks and variables reveal the most robust differences between phobics and matched healthy controls, if there were variables that would provide a "clean break" between affected and non-affected individuals, while simultaneously assessing to what extent participants' behavior depended on their fear levels.

MATERIALS AND METHODS

Participants

In this study, we investigated 32 female participants. One participant was excluded from the analyses because she had severe fear of the control stimulus, resulting in 31 participants (age: $M = 24.5$, $SD = 4.3$, range = 18–35).

Participants were recruited between December 2020 and August 2021 through announcements for people with fear of spiders and announcements for healthy controls on our website and social media. Independent of the announcement, all participants filled out an online screening questionnaire to check the inclusion criteria: aged 18–35, healthy, non-smoker, right-handed, non-pregnant, and a Composite International Diagnostic Screener (CID-S; Wittchen et al., 1999) score below five. Additionally, their severity of spider phobia was assessed by the four items Fear of Spiders Screening (Rinck et al., 2002) in order to control severity distribution and to allow stratification into the extremes "very strong fear of spiders" and "no fear of spiders at all." Eligible participants were automatically redirected for appointment.

The participants were assigned to the phobic group or non-phobic group using the Composite International Diagnostic Interview (CIDI; Wittchen and Pfister, 1997). However, as shown in **Figure 2A**, some of the non-phobic participants had Fear of Spider Questionnaire (FSQ, Szymanski and O'Donohue, 1995) scores above eight, meaning that not all of them were free of fear of spiders (Rinck and Becker, 2007). To be able to examine these differences as well, we further subdivided this non-phobic group and partitioned the whole sample into three groups based on the results of the CIDI and the FSQ score: *phobics* ($N = 15$, age: $M = 24.9$, $SD = 5.0$) who fulfilled the DSM-IV criteria for animal type specific phobia of spiders according to the CIDI; *fearfuls* ($N = 6$, age: $M = 24.0$, $SD = 5.4$) who did not fulfill the DSM-IV criteria but had an FSQ score greater than eight; *non-fearfuls* ($N = 10$, age: $M = 24.3$, $SD = 2.5$) who were both not spider phobic and who had FSQ scores less or equal to eight, as in Rinck and Becker (2007). According to the CIDI, as well as the BDI and CID-S scores, no participant of the non-fearfuls had a psychiatric disorder, and five participants of the phobics had one or two comorbid anxiety disorders (see 1 Comorbidities in **Supplementary Material** for more details).

The study was conducted in accordance with the Declaration of Helsinki (seventh revision, 2013) and approved by the Local Ethics Committee at the Faculty of Medicine at Ludwig Maximilian University of Munich (reference number: 18–403).

Procedure

One day before participation, participants filled out an online questionnaire at home consisting of the Big Five Inventory (BFI, Rammstedt and Danner, 2017), Anxiety Sensitivity Index 3 (ASI, Kemper et al., 2009), Trait Anxiety (TAI, Spielberger, 1983), Beck-Depression Inventory II (BDI, Kühner et al., 2007), Fear of Spiders Screening (SAS, Rinck et al., 2002), Fear of Spider Questionnaire (FSQ, Szymanski and O'Donohue, 1995; Rinck et al., 2002), assessment of disgust sensitivity (FEE, Schienle et al., 2002), Short Scale for the Assessment of Locus of Control (IE-4, Kovaleva et al., 2014), Rosenberg's global Self-Esteem (RSES, Ferring and Filipp, 1996), competence and locus of control (FKK, Krampen, 1991), Sensation Seeking Scales, Form V (SSSV, Beauducel et al., 2003), and the CID-S (Wittchen et al., 1999). Further details on the questionnaires used can be found in **Supplementary Table 3**.

Due to the Covid19 pandemic, hygiene requirements changed in the meantime and led to some, but not all, participants taking a Covid19 test when they arrived and wearing a FFP2 mask during the preparations and the Composite International Diagnostic Interview (CIDI; Wittchen and Pfister, 1997). No masks were worn during the VR session.

Participants arrived either at 1 pm or at 3:30 pm. They were informed about the procedure and gave their written informed consent. Next, the electrodes for the one channel eMotion Faros 180 electrocardiography device from BioSign and the 18 sensors of the Perception Neuron V2 motion tracking system were attached to the torso, limbs, and head and then calibrated (see Binder and Spoormaker, 2020 for details). The participants put on the HTC Vive Pro + Eye VR goggles and the HTC in-ear headphones and the automated procedure was started. The original headphones of the HTC Vive Pro were not used as they disturbed the functioning of the motion tracking system.

From this moment on, all tasks and instructions in iVR were fully automatized, and the participants were instructed not to ask questions, except for urgent ones (no one did). The procedure started with the HTC Vive eye tracking calibration, which set up the inter pupil distance and calibrated the eye-tracking through a two-dimensional five-point calibration. It was followed by a short three-dimensional eye-tracking validation task. Next, pupil size was calibrated by alternately displaying different colors on the screen in the goggles. Afterward, the participants were instructed to behave in the VR as in the real world and not to walk through virtual objects, as they could represent real ones. The introduction continued with some tasks to familiarize participants with navigation and item collection as described in Binder and Spoormaker (2020). At the end of the introduction, the spider and the turtle were sequentially presented in a small side room behind a glass pane (see **Figure 1A**). It was also demonstrated and explained that the animals were always marked with a big blue arrow above them, pointing down at them. The arrow disappeared once the participant looked at the stimulus. This was done to assure participants that there were no hidden spiders that could surprise them. After each presentation, the participants were asked to rate the valence of the animal on a five-point Likert scale. The introduction was finished after the valence-ratings of the animals. The behavioral tasks as described below (2.4 Behavioral Tasks) followed, in the fixed order: Fishing, Path-Choice, and Touch the Enemy. This order was chosen to gradually decrease the degrees of freedom and increase the task intensity. After the last behavioral task, a final scene followed, in which participants were seated and took off the goggles.

After the VR session all sensors were detached, and the participants filled out the post-VR questionnaire on a tablet device. The questionnaire consisted of a visual anxiety scale (ordinal: 0 = "not at all," 10 = "extremely anxious"), valence ratings of the animals (ordinal: 0 = "unpleasant," 10 = "pleasant"), an evaluation of the duration in VR, the Simulator Sickness Questionnaire (SSQ, Kennedy et al., 1993), the Presence Questionnaire 3 (PQ3, Witmer et al., 2005), the iGroup Presence Questionnaire (IPQ, Schubert et al., 1999), and a final question to assess the nervousness on arrival. Finally, the anxiety section of the CIDI was conducted by a trained person (FB). The procedure was completed by filling out the reimbursement form for 30 EUR for participation.

Virtual Reality

The VR was generated in Unity 3D Pro (version: 2020.2.2f1). We used the same setup and scenarios with a field of 4.6 m × 4.3 m, as in Binder and Spoormaker (2020). Instead of fear conditioned balloons, we used a spider ("Giant Spiders Animated," version 1.0.0, "spider_hi_004" scaled by 0.03, length: 8 cm, **Figure 1C**) as aversive stimulus and a turtle (Chinese box turtle, version 1.0.4, "PondTurtleMiddlePoly" scaled by 0.7, size: length: 14 cm, **Figure 1F**) as neutral stimulus, which were purchased in the Unity 3D asset store.

Behavioral Tasks

Behavioral Search Task ("Fishing")

The participants were standing in 80 cm deep non-transparent water, surrounded by wooden planks that indicated the borders of the field (see **Figure 1B** and **Supplementary Video 1**). They started at the edge, centered in front of one of the long sides, facing the center of the field. They were instructed that there were fish in the water, which could neither be seen directly nor were there any hints indicating their position. The task was to catch them with the hand net in the right hand and to put them into the bucket on the plank opposite the starting position. On each of the left or right wood planks was either the spider or the turtle placed in the center. These positions were counterbalanced between participants. After the instruction, the participants had to wait 10 s before fishing for 2 min. They could not catch any fish within this time as to not influence their behavior by success. To still finish the task with a sense of accomplishment, a fish was placed in the hand-net, when it was underwater for 0.5 s after the 2 min, regardless of the participant's position.

The difference between the minimum distance to the spider and the minimum distance to the turtle during the 2 min was used as readout of this task.

Behavioral Forced-Choice Task ("Path-Choice")

The participants were standing in a lobby surrounded by a counter and had to move a book from the counter to a shelf (see **Figure 1D** and **Supplementary Video 2**). They started by the shelf, facing the counter. In front of them was a table, which could be passed either on the left or on the right side. The spider and the turtle were each placed on one side on the outside table of the counter, so the participants had to walk between one of the animals and the table to get to the book. There were five trials with one book each and the positions of the animals swapped after the first and the third trial. The initial positions were counterbalanced between participants. However, only the book of the first trial was placed in the center. The book was placed to the right in the second trial and to the left in the third trial, and far to the right in the fourth trial and far to the left in the fifth trial (see **Figure 1D**). In this way, we could add a certain "cost of avoidance" by making one of the paths the shorter or the longer detour compared to the other.

The avoidance score was calculated to quantify the avoidance of the spider considering the cost of avoidance. The sum of the avoided paths was calculated, where the paths were exponentially weighted by the cost of avoidance: 0, if the shorter path was taken; 1, for equal paths; 2, if the shorter detour was taken; 4, if the longer detour was chosen. If the turtle path was chosen, the weight was set negative. Note that for each trial, we evaluated the outward and return journey separately, yielding a sum of ten paths and a score within the range of −14, if they never avoided the spider, and 14, if they always avoided the spider. In this way, the score is symmetrically distributed and indicates the preference for spider or turtle.

Behavioral Approach Task ("Touch the Enemy")

The participants were in a room with a door and a large window with closed blinds (see **Figure 1E** and **Supplementary Video 3**). They started at the edge of one wall facing the center of the room. In front of the opposite wall was a small round table at a height of 1.1 m presenting one of the animals at a time. The participants were instructed to walk to the object and touch it with the right hand, as soon as the countdown of 10 s finished. Each animal was presented twice in an alternating manner, resulting in four trials. The animal type of the first trial was counterbalanced between participants.

For each trial, we defined the time to touch as the time from the end of the countdown to the touch of the animal. As readout of this task, we used the difference of the time to touch between the first spider trial and the first turtle trial. A positive readout means that the participant took more time to touch the spider the first time compared to the turtle the first time. Six values in the phobics (21, 22, 30, 39, 70, and 212 s) were truncated to 20 s.

Statistics

All statistics were performed in MathWorks Matlab R2021a. The Matlab-toolbox "Measures of Effect Size" version 1.6.1

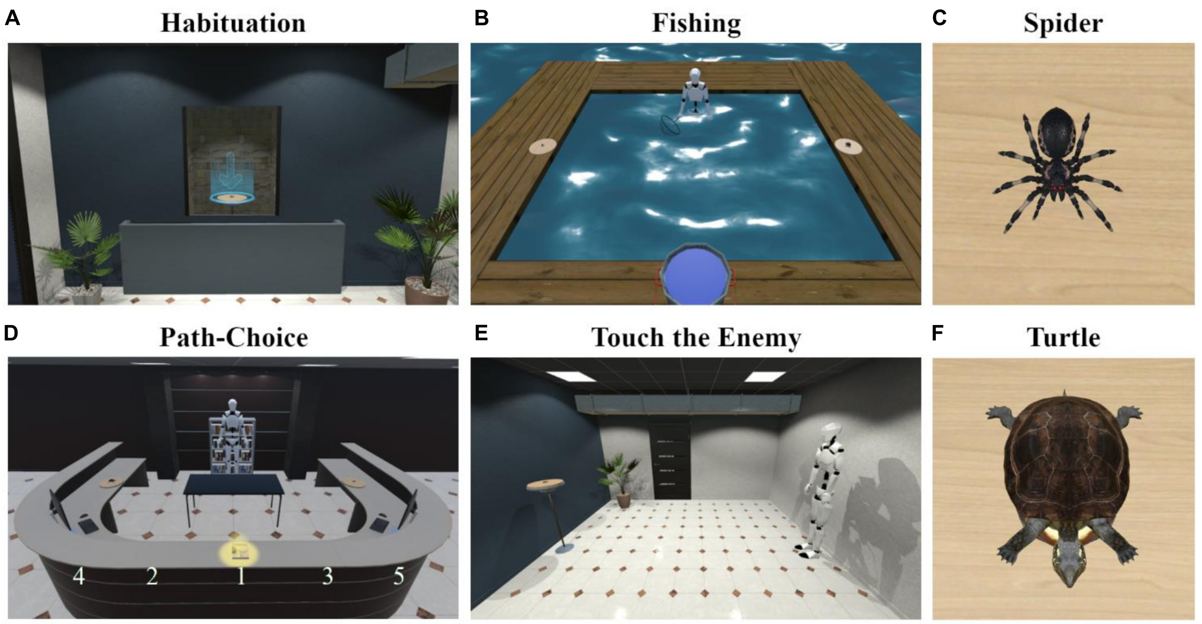

FIGURE 1 | Screenshots of the virtual reality scenes: **(A)** Habituation—first person view of the stimulus habituation with the blue arrow being present, **(B)** Fishing—the behavioral search task, **(C)** Spider—the aversive stimulus, **(D)** Path-Choice—the behavioral forced-choice task, the white numbers indicate the book position of the respective trial, **(E)** Touch the Enemy—the behavioral approach task, **(F)** Turtle—the control stimulus.

(Hentschke and Stüttgen, 2011) was used to calculate the effect sizes Cohen's U3 for Mann–Whitney *U*-tests, the η^2 for analyses of variance, Hedges' g_1 for one sample *t*-tests, and Glass' Δ for two sample *t*-tests. The partial-eta-squared (η_p^2) and generalized-eta-squared ($\eta^2{}_G$) were calculated by us for repeated measure analyses of variance (rmANOVA) (Olejnik and Algina, 2003; Bakeman, 2005). In all tests, an alpha level of 0.05 was used for significance. The figures were generated with the Matlab toolbox "Gramm" (Morel, 2018).

Physiology

Eye data were recorded in Unity at a sampling rate of approximately 110 Hz using the VIVE Eye and Facial Tracking SDK (SRanipal version 1.3.2.0).

Pupil size was preprocessed in Matlab: first, outliers were removed, defined as values that were more than three scaled absolute deviations away from the moving median with a window size of 100 samples. Then, missing values resulting from outlier detection and closed eyes were linearly interpolated and the pupil size was resampled to regular 110 Hz using the "nearest" method. Finally, the data were rescaled to an interval of zero to one.

The gaze data was recorded in Unity: In each frame, the most recently available eye data from both eyes was used and combined with head position and rotation to determine the direction of gaze in three-dimensional VR. This was used for collision detection with virtual objects to determine the focused object. Later in Matlab, when the time series of the focused object was used to determine the viewing duration and the number of glances at an object of interest, viewing gaps of less than 200 ms, during which no focus on the object was detected, were considered continuous.

The electrocardiography signal was analyzed in Matlab using the PhysioNet-Cardiovascular-Signal-Toolbox (version 1.0.2; Vest et al., 2019) as described in Binder and Spoormaker (2020) resulting in a timeseries of RR intervals, which represent the duration between successive heartbeats, stored at 250 Hz.

Behavioral Tasks

Based on the construction, we assumed a continuous scale level for the readouts of the Fishing and Touch the Enemy tasks and an ordinal scale level for the readout of the Path-Choice task. Accordingly, we calculated ANOVAs with *post hoc t*-tests and Pearson correlations for the Fishing and Touch the Enemy tasks. For the Path-Choice tasks we performed the Kruskal–Wallis test with *post hoc* Mann–Whitney-*U* tests and spearman correlations.

In the Fishing task, a repeated measure ANOVA (rmANOVA) was performed with group as the between-factor and stimulus as the within-factor to analyze the number of glances at the stimuli in an explorative manner. *Post hoc*, the within-subject difference between the number of glances at the spider and the number of glances at the turtle was compared between groups using independent *t*-tests and Pearson correlated with the FSQ score. To explore participants orientation during the Fishing task, the mean angle between the hip and the respective stimulus was calculated for each side. An angle of zero or 180 means that the hips were aligned with the front or back side to the stimulus, respectively. As with the analyses of the number of glances, they were analyzed by rmANOVA, independent *t*-tests and Pearson correlation. Four participants (two phobics and two fearfuls) were excluded from these analyses because they never entered the side with the spider. For each participant, the RR interval and pupil size per stimulus side were defined as the mean over time while on the pelvic half with the corresponding stimulus.

To examine Touch the Enemy times in detail, the path from the start position to the stimulus was divided into three equal areas and the time spent in each area was determined. These durations were analyzed by rmANOVA with group as between-factor and trial, stimulus, and area as within-factors. Furthermore, to gain insight into the directness and automation of the approach movements, the changes in acceleration of the right hand were analyzed: First, the irregular right-hand position for each frame were down sampled to regular 10 Hz samples using spline interpolation. Second, the number of sign changes of the second derivative of these data was determined for each trial and used as the number of changes in acceleration. Seven values, in the phobic group (111, 124, 147, 181, 241, 251, and 739) were truncated to 100. The number of changes in acceleration were analyzed with a rmANOVA with group as the between-factor, and trial and stimulus as the within-factor. The pre-touch pupil size was defined as the mean preprocessed pupil size of the right eye in the 0.5 s before the stimulus was touched and analyzed with a rmANOVA with group as the between-factor, and trial and stimulus as the within-factor. One participant of the phobic group was excluded from this analysis as she closed her eyes before touching the spider. Similarly, the pre-touch RR interval was defined as the mean RR interval in the last second before the stimulus was touched and analyzed with a rmANOVA with the same factors. Here, eight participants were excluded because of missing data.

Across Tasks Analyses

To investigate the consistency in behavior, Spearman correlations between the readouts of the three behavioral tasks were calculated. Spearman correlations were also used to examine the relations between the behavioral readouts and subjective data from the online home questionnaire and the post-VR questionnaire. To account for multiple testing, the significance level ****, representing the conservative Bonferroni corrected $p < 0.00031 = 0.05/(3 \times 54)$, was added. In addition, as many of the questionnaire scales were also Spearman correlated with the FSQ and the valence rating of the spider, partial Spearman correlations were calculated between the behavioral readouts and the subjective data, controlling for either the FSQ or the valence rating.

RESULTS

Manipulation Check

The participants felt highly present in the VR as rated in the Presence Questionnaire 3 (Mean ± SD, range: 1–7, 7 = best): involvement, 5.4 ± 0.7; sensory fidelity, 5 ± 0.8; adaptation immersion, 5.9 ± 0.6; interface quality (1 = best), 2.1 ± 0.9; and in the iGroup Presence Questionnaire (range: 0–6, 6 = best): general presence, 4.5 ± 1.2; spatial presence, 4.8 ± 0.7; involvement, 4.6 ± 1.0; experienced realism, 2.9 ± 1.1. Moreover, they reported only slight side effects in the SSQ (approximate theoretical range: 0–200, 0 = best): total score, 19.7 ± 25.0; nausea, 18.5 ± 30.5; oculomotor symptoms, 12.5 ± 13.5; disorientation, 23.3 ± 34.5.

The difference in the valence ratings of the turtle and the spider was analyzed with the Kruskal–Wallis test and revealed an effect of group [$X^2(2, N = 31) = 17.2$, $p < 0.001$]. The *post hoc* group comparisons revealed significant differences between phobics and fearfuls [$U(n_1 = 15, n_2 = 6) = 76.5$, $p < 0.05$, $U3 = 0.07$], and between phobics and non-fearfuls [$U(n_1 = 15, n_2 = 10) = 142.5$, $p < 0.001$, $U3 = 0.00$], but not between fearfuls and non-fearfuls [$U(n_1 = 10, n_2 = 6) = 46$, $p = 0.08$, $U3 = 0.08$]. The differences in the valence ratings of the stimuli were strongly correlated with the FSQ scores ($r_s = 0.67$, $p < 0.001$). The relationship is depicted in **Figure 2B**.

Behavioral Tasks

Fishing

The individual difference in the minimum distance to the spider and the minimum distance to the turtle during the 120 s was analyzed with an ANOVA. It revealed an effect of group [$F(2,28) = 11.62$, $p < 0.001$, $\eta^2 = 0.45$]. The *post hoc t*-test revealed increased avoidance behavior for phobics compared to non-fearfuls [$t(23) = 5.17$, $p < 0.001$, $\Delta = 1.74$] and for fearfuls compared to non-fearfuls [$t(14) = 3.65$ $p < 0.01$, $\Delta = 1.21$], but no differences between phobics and fearfuls [$t(19) = 0.09$, $p = 0.93$, $\Delta = 0.05$]. The readout of the Fishing task was strongly correlated with the FSQ score ($r = 0.57$, $p < 0.001$). The differences in the minimal distance to the stimuli as related to participants' FSQ scores and group membership is depicted in **Figure 3**.

The number of glances at the stimuli was analyzed with an ANOVA and revealed a group effect [$F(2,28) = 5.82$, $p < 0.01$, $\eta_p^2 = 0.29$, $\eta_G^2 = 0.21$], a stimulus effect [$F(1,28) = 10.87$, $p < 0.01$, $\eta_p^2 = 0.19$, $\eta_G^2 = 0.13$], and a stimulus × group interaction [$F(2,28) = 9.51$, $p < 0.001$, $\eta_p^2 = 0.29$, $\eta_G^2 = 0.20$]. The *post hoc* group comparisons revealed an increased number of glances at the spider for phobics compared to fearfuls [$t(19) = 2.18$, $p < 0.05$, $\Delta = 0.96$] and for phobics compared to non-fearfuls [$t(23) = 4.16$ $p < 0.001$, $\Delta = 1.30$], but no differences between fearfuls and non-fearfuls [$t(14) = 1.36$, $p = 0.19$, $\Delta = 0.42$]. The difference in the number of glances at the stimuli was strongly correlated with the FSQ score ($r = 0.57$, $p < 0.001$). The number of glances at the stimuli is depicted in **Figure 4A**.

The analysis of participants' orientation toward the stimuli revealed a group effect [$F(2,24) = 4.48$, $p < 0.05$, $\eta_p^2 = 0.27$, $\eta_G^2 = 0.22$], a stimulus effect [$F(1,24) = 6.13$, $p < 0.05$, $\eta_p^2 = 0.08$, $\eta_G^2 = 0.06$], and a stimulus × group interaction [$F(2,24) = 8.77$, $p < 0.01$, $\eta_p^2 = 0.21$, $\eta_G^2 = 0.16$]. The *post hoc* group comparisons revealed a smaller angle toward the spider for phobics compared to non-fearfuls [$t(21) = -4.53$ $p < 0.001$, $\Delta = -1.69$], but no differences between phobics compared to fearfuls [$t(15) = -1.27$, $p = 0.22$, $\Delta = -0.76$] and fearfuls compared to non-fearfuls [$t(12) = -1.63$, $p = 0.13$, $\Delta = -0.63$]. The difference in orientation was strongly correlated with the FSQ score ($r = -0.63$, $p < 0.001$). The orientations are depicted in **Figure 4B**.

Participants' heart rate expressed as RR interval per stimulus side during the Fishing task was analyzed with a rmANOVA, which revealed neither a group effect [$F(2,24) = 3.12$, $p = 0.06$,

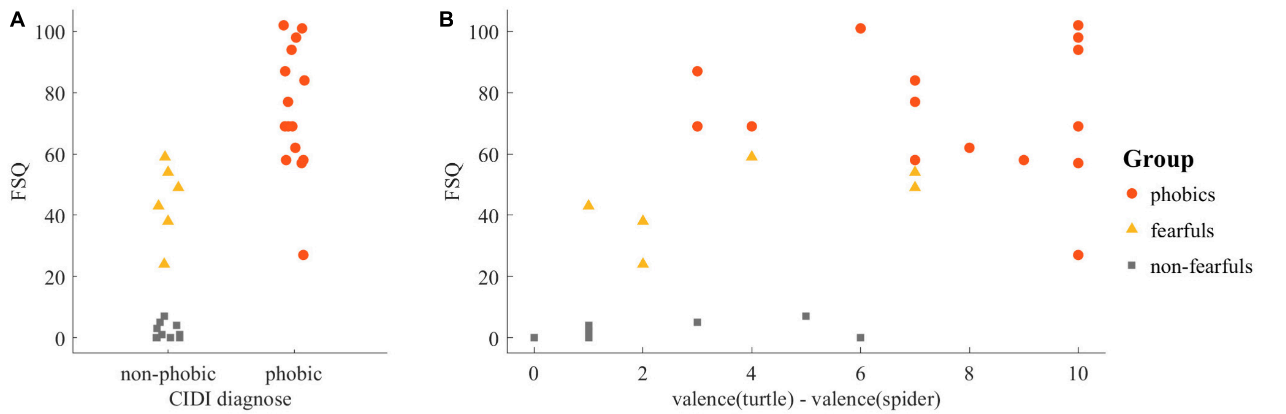

FIGURE 2 | Sample description: **(A)** Diagnosis for spider phobia of the Composite International Diagnostic Interview in association with the Fear of Spiders Questionnaire (FSQ) yielded three clusters that formed the basis for the groups. **(B)** The difference in the valence rating of the turtle and the valence rating of the spider in association with the FSQ.

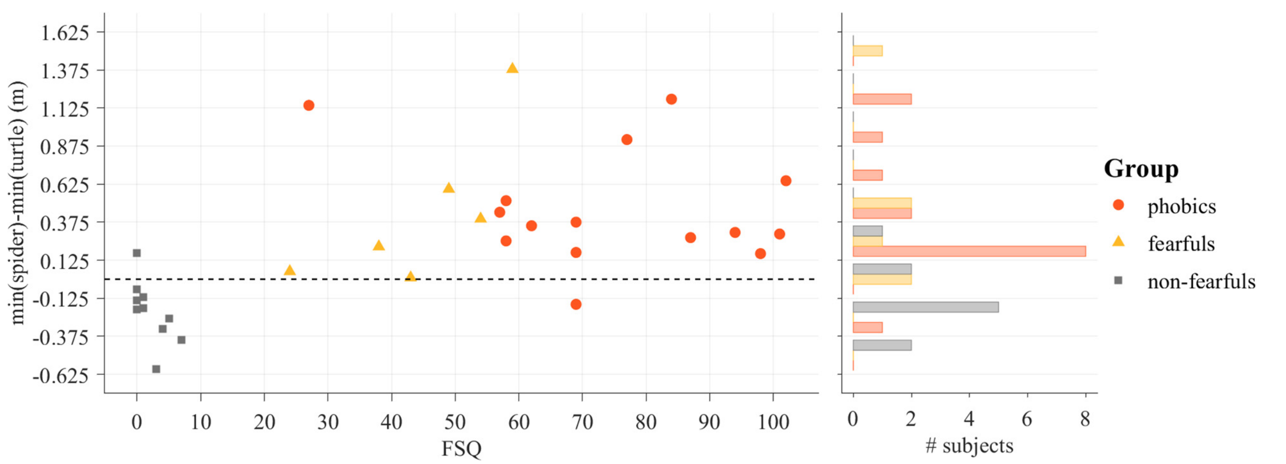

FIGURE 3 | The result of the Fishing task dependent on the Fear of Spiders Questionnaire (FSQ) score (left) and accumulated in a histogram (right).

η_p^2 = 0.21, η_G^2 = 0.20], nor a stimulus effect [F(2,24) = 0.001, p = 0.97, η_p^2 < 0.001, η_G^2 < 0.001], nor a group × stimulus interaction [F(2,24) = 2.85, p = 0.08, η_p^2 = 0.01, η_G^2 = 0.01]. The heart rate expressed as RR interval is depicted in **Figure 5A**. Albeit the non-significant group effect, we performed direct group comparisons to explore the trends in the data, well-knowing that these were no regular *post hoc* tests. **Figure 5B** depicts the spider-turtle differences by group and independent t-tests revealed a difference between phobics and non-fearfuls [t(21) = −2.22, p < 0.05, Δ = −2.07], meaning that RR intervals decreased and thus heart rate was increased in the phobics group when on the side with the spider. We did not find any differences or trends in the mean pupil size (all p > 0.50 in rmANOVA).

Path-Choice

The avoidance score was analyzed with the Kruskal–Wallis test and revealed an effect of group [$X^2(2, N = 31)$ = 15.70, p < 0.001]. The *post hoc* group comparisons revealed significant differences between phobics and non-fearfuls [$U(n_1 = 15, n_2 = 10)$ = 138.5, p < 0.001, $U3$ = 0.07], between fearfuls and non-fearfuls [$U(n_1 = 10, n_2 = 6)$ = 53.5, p < 0.05, $U3$ = 0.07], but not between phobics and fearfuls [$U(n_1 = 15, n_2 = 6)$ = 68, p = 0.07, $U3$ = 0.27]. The avoidance score was strongly correlated with the FSQ score (r_s = 0.70, p < 0.001). The avoidance scores as related to participants' FSQ scores, and group membership is depicted in **Figure 6**.

Touch the Enemy

The difference in the time to touch the spider and the time to touch the turtle was analyzed with an ANOVA and revealed an effect of group [F(2,28) = 13.34, p < 0.001, η^2 = 0.49]. The *post hoc* t-tests revealed increased avoidance behavior for phobics compared to fearfuls [t(19) = 2.67, p < 0.05, Δ = 1.09] and for phobics compared to non-fearfuls [t(23) = 4.57 p < 0.001, Δ = 1.44], but no differences between fearfuls and non-fearfuls [t(14) = 2.07, p = 0.06, Δ = 0.81]. The readout of the Touch the

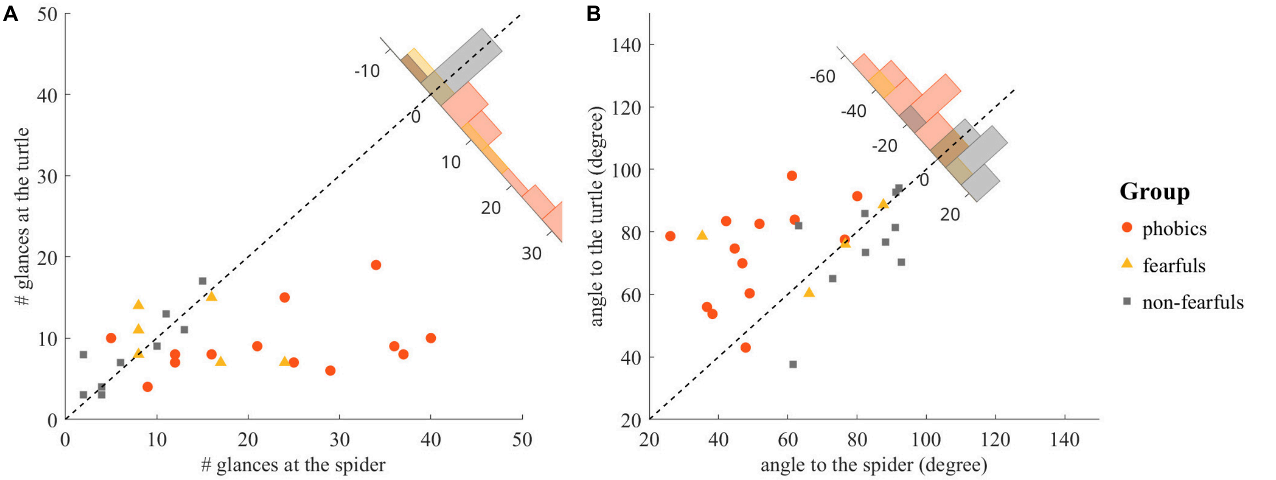

FIGURE 4 | Detailed analyses of the Fishing task: **(A)** Comparison of the number of glances at the spider and the number of glances at the turtle, including the histogram of individual differences in the upper right corner. **(B)** Comparison of the angle between the chest front and the spider and the angle between the chest front and the turtle, including the histogram of individual differences in the upper right corner. The angle was 0 if the chest front was facing the animal and 180 when it was facing away from the animal.

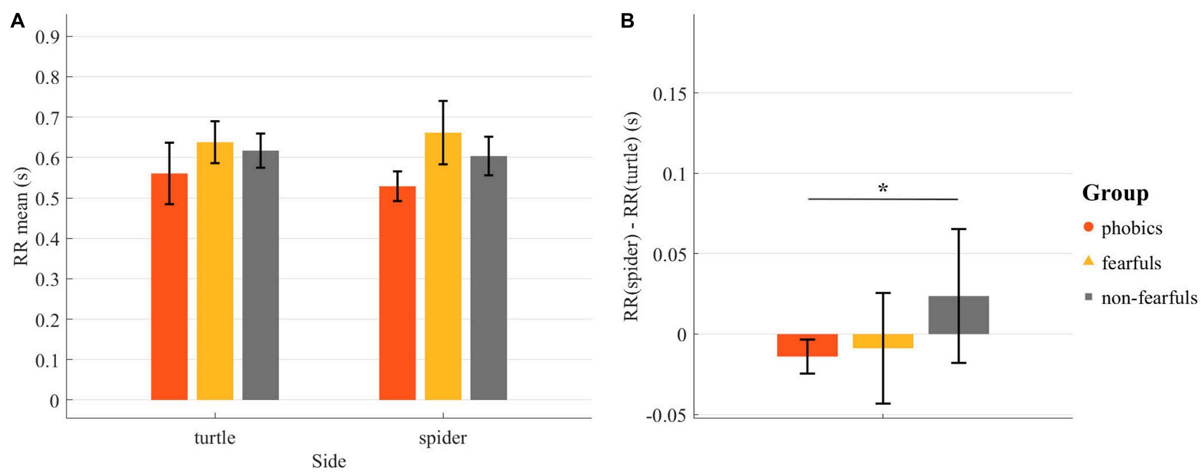

FIGURE 5 | Heart rate analyses during the Fishing task: **(A)** The mean RR interval in seconds per stimulus side while they stayed there. **(B)** The individual differences between the mean RR interval on the spider side and the mean RR interval on the turtle side. Bars = group mean; lines = standard error; RR interval = heartbeat to heartbeat duration; $^{*}p < 0.05$.

Enemy task was strongly correlated with the FSQ score ($r = 0.67$, $p < 0.001$). The differences in the time to touch the stimuli as related to participants' FSQ scores and group membership is depicted in **Figure 7**.

The duration spent in each third during the Touch the Enemy task was analyzed with a rmANOVA and revealed an effect of group [$F(2,28) = 8.43$, $p < 0.01$, $\eta_p^2 = 0.38$, $\eta_G^2 = 0.12$], trial [$F(2,28) = 11.02$, $p < 0.01$, $\eta_p^2 = 0.05$, $\eta_G^2 = 0.01$], stimulus [$F(2,28) = 12.50$, $p < 0.01$, $\eta_p^2 = 0.27$, $\eta_G^2 = 0.08$], and area [$F(2,56) = 33.63$, $p < 0.001$, $\eta_p^2 = 0.52$, $\eta_G^2 = 0.20$]. The interactions with the three largest effects revealed by the rmANOVA were group × area [$F(4,56) = 9.52$, $p < 0.001$, $\eta_p^2 = 0.38$, $\eta_G^2 = 0.13$], group × stimulus [$F(2,28) = 9.61$, $p < 0.001$, $\eta_p^2 = 0.36$, $\eta_G^2 = 0.12$], and group × stimulus × area [$F(4,56) = 10.56$, $p < 0.001$, $\eta_p^2 = 0.36$, $\eta_G^2 = 0.12$]. A complete list of statistics can be found in **Supplementary Table 4**. The durations are depicted in **Figure 8**.

The number of changes in acceleration was analyzed with a rmANOVA and revealed an effect of group [$F(2,28) = 8.20$, $p < 0.01$, $\eta_p^2 = 0.37$, $\eta_G^2 = 0.23$], trial [$F(1,28) = 10.06$, $p < 0.01$, $\eta_p^2 = 0.05$, $\eta_G^2 = 0.02$], and stimulus [$F(1,28) = 12.18$, $p < 0.01$, $\eta_p^2 = 0.24$, $\eta_G^2 = 0.13$] and a group × stimulus interaction [$F(2,28) = 8.73$, $p < 0.01$, $\eta_p^2 = 0.31$, $\eta_G^2 = 0.18$]. No interactions of group × trial [$F(2,28) = 1.73$, $p = 0.20$, $\eta_p^2 = 0.02$, $\eta_G^2 = 0.01$], stimulus × trial [$F(1,28) = 0.93$, $p = 0.34$, $\eta_p^2 = 0.01$, $\eta_G^2 < 0.01$],

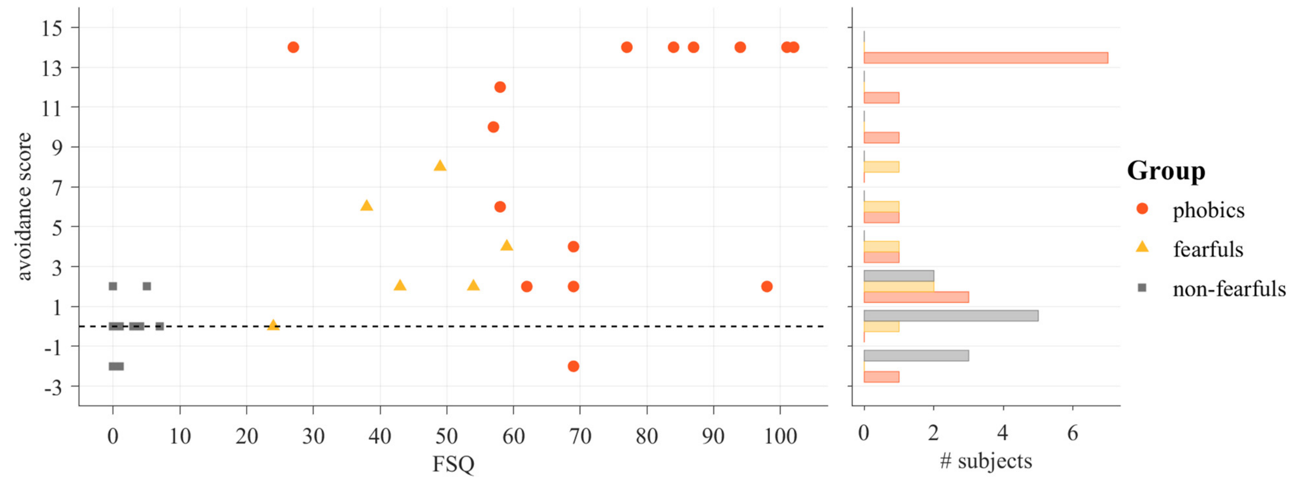

FIGURE 6 | The result of the Path-Choice task dependent on the Fear of Spiders Questionnaire (FSQ) score (left) and accumulated in a histogram (right).

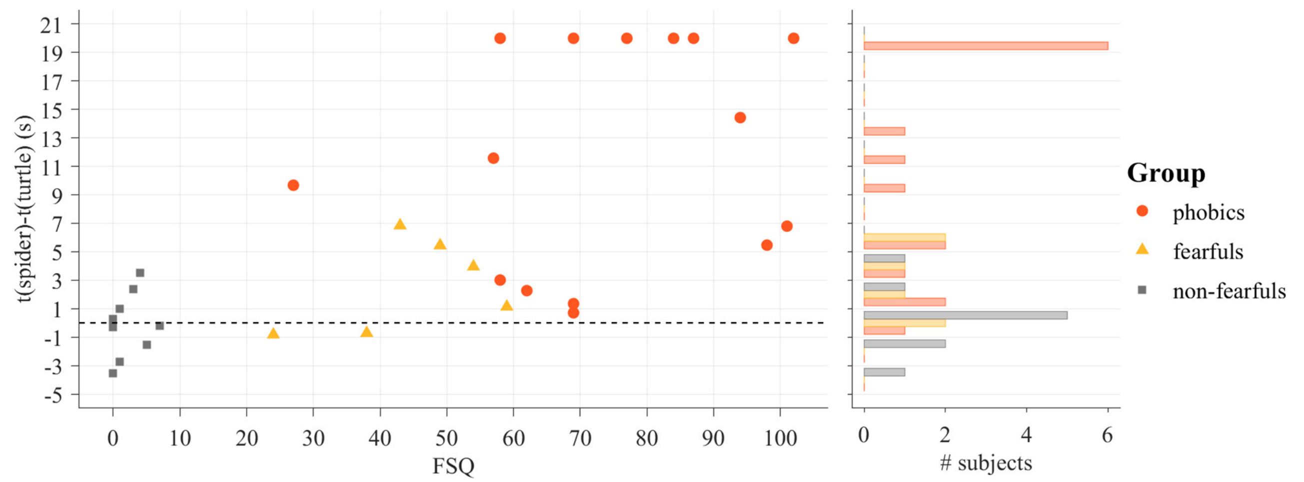

FIGURE 7 | The result of the Touch the Enemy task dependent on the Fear of Spiders Questionnaire (FSQ) score (left) and accumulated in a histogram (right). Individual values were truncated to 20 s.

or group × stimulus × trial [$F(2,28) = 0.84$, $p = 0.44$, $\eta_p^2 = 0.01$, $\eta_G^2 = 0.01$] were observed. The number of changes in acceleration by stimulus and group is depicted in **Figure 9**.

The pre-touch pupil size was analyzed with a rmANOVA and revealed a stimulus × group interaction [$F(2,27) = 3.51$, $p < 0.05$, $\eta_p^2 = 0.05$, $\eta_G^2 = 0.03$], showing a stronger pupil dilation to the spider in the phobics group. No other effects or interactions were significant. The pre-touch pupil size by group, stimulus, and trial is depicted in **Figure 10A**. The pre-touch heart rate expressed as RR interval was also analyzed with a rmANOVA and revealed no significant effects or interactions. However, we also found a trend in the group × stimulus interaction [$F(2,20) = 1.21$, $p = 0.32$, $\eta_p^2 = 0.02$, $\eta_G^2 = 0.02$], indicating a decreased RR interval and thus an increased heart rate to the spider in the phobics group. The pre-touch RR interval by group, stimulus, and trial is depicted in **Figure 10B**.

Across Tasks Analyses

The tasks Fishing and Path-Choice ($r_s = 0.75$, $p < 0.001$), Fishing and Touch the Enemy ($r_s = 0.63$, $p < 0.001$), and Path-Choice and Touch the Enemy ($r_s = 0.72$, $p < 0.001$) were strongly correlated. The tasks consistency is depicted in **Figure 11**.

The correlations of the behavioral tasks and the questionnaire scales are shown in **Table 1**. In the last two columns, we added the correlation between the questionnaire scales and either the FSQ or the valence rating of the spider. The visual anxiety scale, the BDI, the valence rating of the spider and some scales of the SSQ and ASI were correlated with the readouts of all behavioral tasks. As these scales were also correlated with the FSQ, partial correlations between the questionnaire scales and the behavioral readouts controlled for the FSQ were calculated. The significant correlations

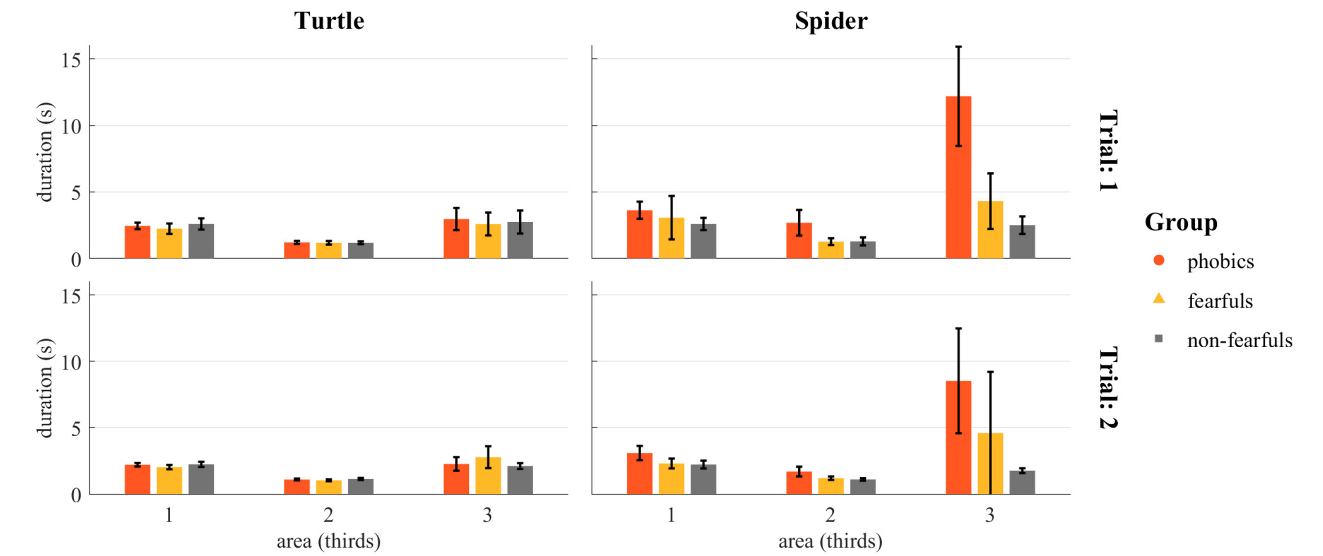

FIGURE 8 | Detailed analyses of the touch duration in the Touch the Enemy task: The duration in seconds the participants stayed on the way to the stimulus in each third. Individual values were truncated to 20 s. The rmANOVA revealed significant main effects of group, trial, stimulus, and area, and significant group × trial, group × stimulus, group × area, group × trial × area, stimulus × area, and group × stimulus × area interactions. Bars = group mean; lines = standard error.

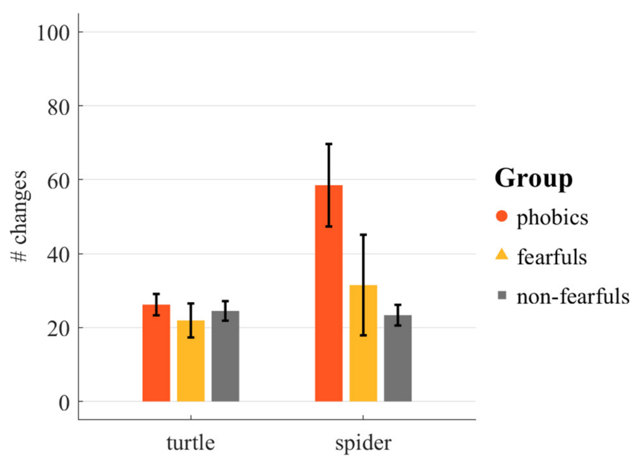

FIGURE 9 | The number of changes in acceleration of the right hand on the way to the stimulus in the Touch the Enemy task. The individual values were truncated to 100. The rmANOVA revealed a significant main effect of group, stimulus, and trial, and a significant group × stimulus interaction. Bars = group mean; lines = standard error.

are marked in **Table 1** and the details are reported in **Supplementary Table 5**. Interestingly, when controlling for the valence of the spider, only the two scales nausea (r_s = 0.39, $p < 0.05$) from the SSQ and conscientiousness (r_s = 0.37, $p < 0.05$) from the BFI were significantly partially correlated with the avoidance score of the Path-Choice task, but none of the correlations with the two other tasks survived. A complete list of these partial correlations can be found in **Supplementary Table 6**.

DISCUSSION

We evaluated which of the tasks and variables would reveal the most robust differences between phobics and matched healthy controls while simultaneously assessing to what extent participants' behavior depended on their fear levels. As the healthy controls were quite heterogeneous in terms of their Fear of Spiders Questionnaire (FSQ) scores, we subdivided them into "fearfuls" that had elevated FSQ scores, and "non-fearfuls" that had no fear of spiders. We investigated their behavior in the presence of a spider and a neutral animal and found that phobics strongly disliked the spider in iVR, but fearfuls and non-fearfuls rated the spider only slightly more unpleasant than the neutral animal. Across all tasks, spider phobics showed significant avoidance behavior. In the behavioral search task (Fishing), the phobics and fearfuls strongly avoided the spider, but the non-fearfuls did not. In the behavioral forced-choice task (Path-Choice), the phobics also strongly avoided the spider, but the non-fearfuls did not and the fearfuls showed mild avoidance behavior. In the behavioral approach task (Touch the Enemy), the phobics strongly delayed touching the spider, but the fearfuls and non-fearfuls showed no delay.

The objectively quantified avoidance behavior showed strong correlations with the FSQ in all three tasks. Furthermore, the valence of the spider was strongly correlated with the FSQ and the behavioral readouts of all tasks. This raised the question of the directionality of the effects and prompted us to calculate additional partial correlations. Controlling for the valence rating completely removed the correlation between the FSQ and the behavioral readouts but vice versa the correlations between valence rating and behavioral readouts survived controlling for the FSQ. This suggest that the valence rating of the spider is mediating the relationship between FSQ and avoidance

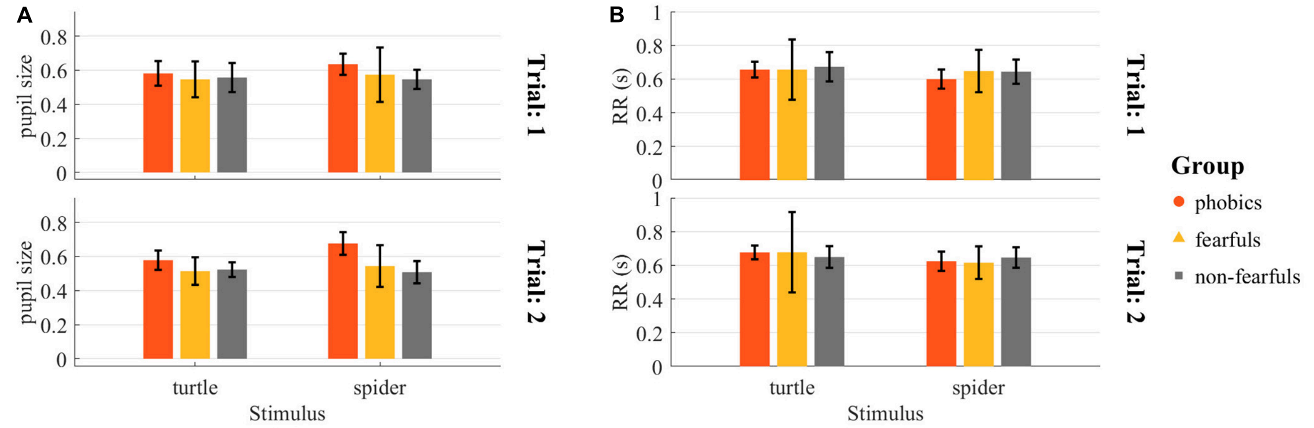

FIGURE 10 | Physiological readouts during the Touch the Enemy task: **(A)** Mean rescaled pupil size during the last 0.5 s before the touch of the stimulus. The rmANOVA revealed a significant group × stimulus interaction. **(B)** Mean RR interval during the last second before the touch of the stimulus. The rmANOVA revealed no significant effects or interactions (all $p > 0.05$). RR interval = heartbeat to heartbeat duration.

behavior. In addition, the valence of the spider was also strongly correlated with the Visual Anxiety Scale and SSQ, which assessed participants' subjective well-being after the VR session. This suggests that the valence of the spider was the main factor influencing both the objective avoidance behavior and the subjective experience of the exposure. The appearance of the spider seems to be the key factor in controlling the intensity of exposure as well as in generalizing fear and extinction learning.

On top of using a two-group design based on the spider phobia diagnosis of the Composite International Diagnostic Interview (CIDI), we additionally split up the non-phobics group into non-fearfuls and fearfuls based on participants' FSQ scores with cut-offs as used in Rinck and Becker (2007), Rinck et al. (2010). This allowed us to better distinguish the fearfuls from phobics and non-fearfuls and provided further insight into the process of adaptive and maladaptive avoidance behavior: while the phobics and non-fearfuls showed consistent avoidance and non-avoidance behavior, respectively, the fearfuls' behavior varied between tasks: in the search task, they showed strong avoidance behavior like the phobics did, but in the approach task they showed no avoidance behavior, and in the forced-choice task they showed moderate avoidance behavior in between the fearfuls and phobics. This suggests that participants with a medium level of fear avoid a feared stimulus if it is irrelevant to the task and the degree of freedom is high, but fear does not influence their behavior if the feared stimulus is relevant for the task. This is in line with our previous study (Binder and Spoormaker, 2020), in which healthy participants showed the same pattern of avoidance behavior toward fear conditioned stimuli across three behavioral tasks. It underlines that the behavioral search task with stimuli being less relevant for the task is the most sensitive one to detect avoidance behavior and the behavioral approach task is less sensitive, but better suited to detect differences for high levels of fear.

More detailed behavioral analyses within the tasks showed that in the behavioral search task, phobics looked more frequently at the spider than at the neutral stimulus, but the fearfuls and non-fearfuls did not. This is in line with attentional bias theory, which postulates that highly-anxious individuals tend to direct attention to fear-related stimuli, whereas low-anxious subjects do not (Mathews and MacLeod, 1985; MacLeod et al., 1986; Bar-Haim et al., 2007; Abado et al., 2020). Furthermore, we explored participants' body orientation and observed that the phobics preferred to have the spider in front of them when they searched at the spider's side. The non-fearfuls and most of the fearfuls did not show this "defensive" behavior. An additional manipulation in the behavioral forced-choice task was the cost of avoidance, which was added in later trials. Despite such costs of avoidance, almost half of the phobics always avoided the spider, but none of the fearfuls or non-fearfuls did. This shows the specific willingness or habit of phobics to accept personal disadvantages to avoid their fear, similarly to what the fearful participants in Pittig et al. (2014) did, when they generally avoided choices associated with pictures of spiders in a gambling task, even when they were offered advantages. In the behavioral approach task when the phobics approached the spider, although they hesitated at the beginning and walked slower in the middle third, the main hesitation occurred in the last third, indicating that fear levels increased with proximity to the spider. This is consistent with the predatory imminence hypothesis, according to which defensive behavior changes depending on the perceived distance to the threat (Fanselow and Lester, 1988). Interestingly, the phobics touched the spider much faster already in the second trial. The explanation given by participants in an unstructured interview at the end of the study was that they "knew" what the spider was doing after the first trial. This raises the question of what they expected beforehand? According to Arntz et al. (1993), beliefs that the spider is coming toward one or jumping onto one as well as self-related beliefs such as losing control are very frequent in spider phobia. This cognitive aspect of specific phobia was also elaborated by Armfield (2006) in the cognitive vulnerability model, according to which perceived controllability,

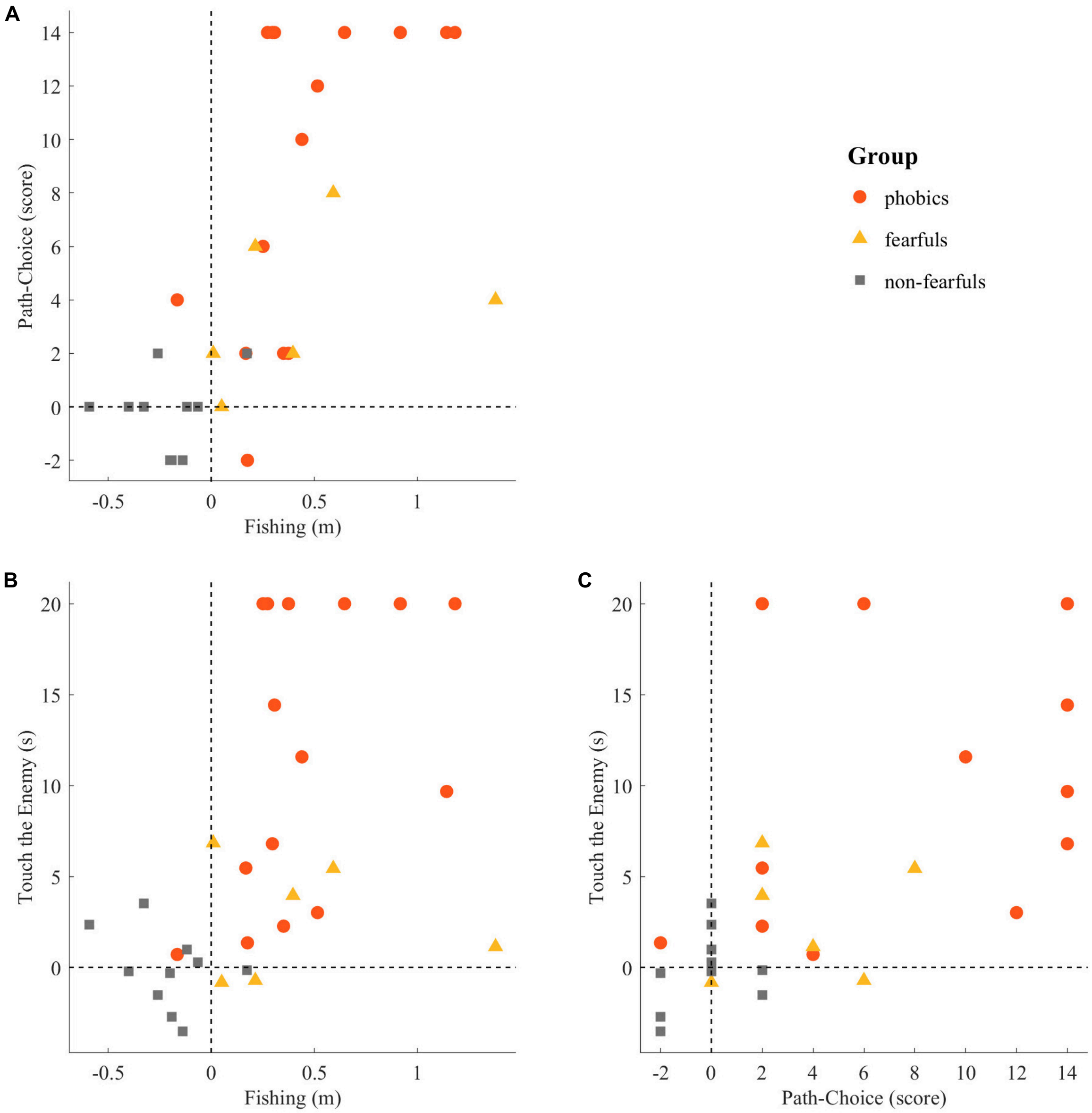

FIGURE 11 | Consistency of behavioral tasks: **(A)** Fishing vs. Path-Choice, **(B)** Fishing vs. Touch the Enemy, and **(C)** Path-Choice vs. Touch the Enemy. Individual values in the Touch the Enemy task were truncated to 20 s. Points represent individual readouts, and dashed lines indicate the boundary between avoidance and approach behavior in each task.

predictability, and dangerousness of a stimulus contribute to the individual's fear. He further showed, that in an imaginary task, especially the manipulation of perceived controllability or predictability of the spider influenced the task-related spider fear (Armfield, 2007). In a meta-analytic review, Gallagher et al. (2014) showed that lower perceived control was associated with anxiety disorders and that perceived control was an important predictor for cognitive-behavior therapy outcome. Similarly, Tardif et al. (2019) showed that changes in perceived self-efficacy and beliefs about spiders were related to the reductions in fear of spiders after exposure in VR. Transferring these insights to our situation led us to speculate that the knowledge gained might have changed the participants' beliefs about spiders, increased the perceived control and thus decreased the avoidance behavior.

Additionally, we investigated the physiological effects of the behavioral approach and search tasks. We found increased pupil size and a trend toward increased heart rate when phobics approached the spider. In the behavioral search task, we found a trend toward increased heart rate when phobics searched in the side of the spider, but no effects on pupil size. In summary, we found physiological activation in response to exposure to the feared stimulus as proposed by emotion processing theories (Lang, 1985; Foa and Kozak, 1986; Barlow, 2002) and already shown *in vivo* (Sartory et al., 1977) as well as in VR (Diemer

TABLE 1 | Spearman correlations between questionnaires and behavioral tasks.

Questionnaire/Scale		Fishing	Path-Choice	Touch the Enemy	FSQ	Valence spider
	Visual anxiety scale	**0.59*****	0.58***	**0.67******	0.53**	−**0.67******
	Nervousness	0.30	**0.36***	**0.32**	0.03	−0.21
	BDI	0.51**	0.31	0.52**	0.56***	−0.57***
	TAI	0.17	−0.03	0.06	0.22	−0.04
	CID-S	0.39*	0.27	0.34	0.54**	−0.32
	SAS	0.67****	0.72****	0.69****	0.93****	−0.75****
	RSES	0.01	**0.07**	−0.11	−0.28	−**0.00**
Valence	Turtle	−0.13	−0.24	0.01	−0.21	0.14
	Spider	−**0.75******	−**0.81******	−**0.80******	−0.78****	**1.00******
	Turtle–Spider	**0.70******	**0.68******	**0.67******	0.67****	−**0.87******
SSQ	Nausea	**0.59*****	**0.67******	**0.61******	0.50**	−**0.59*****
	Oculomotor	0.32	0.47**	0.52**	0.47**	−0.52**
	Disorientation	0.53**	0.46**	0.48**	0.53**	−0.60***
	Total	0.58***	**0.66******	0.65****	0.65****	−**0.71******
PQ3	Involvement	0.03	0.06	0.30	0.21	−0.14
	Sensory Fidelity	−0.13	0.00	0.17	0.02	−0.06
	Adaptation Immersion	−0.16	−0.19	−0.03	−0.11	0.09
	Interface Quality	0.10	−0.10	−0.07	−0.05	0.11
IPQ	General presence	−0.06	−**0.01**	0.14	0.33	−0.18
	Spatial presence	−0.21	−0.11	−0.15	−0.17	0.27
	Involvement	0.01	0.06	0.05	0.06	−0.15
	Experienced realism	0.12	0.04	0.12	0.24	−0.15
BFI	Extraversion	0.24	0.25	0.44*	0.28	−0.35
	Agreeableness	−0.10	0.05	0.01	0.04	0.09
	Conscientiousness	0.16	0.26	0.19	0.05	−0.05
	Neuroticism	0.04	−0.00	0.07	0.00	−0.06
	Openness	0.20	0.07	0.29	0.17	−0.26
ASI	Somatic concerns	0.52**	0.47**	0.45*	0.67****	−0.55**
	Social concerns	0.21	0.27	0.48**	0.54**	−0.46**
	Cognitive concerns	0.32	0.16	0.42*	0.45*	−0.30
	Total	0.45*	0.39*	0.52**	0.63****	−0.53**
SSSV	Thrill and Adventure	−0.29	−0.35	−0.18	−0.29	0.23
	Disinhibition	0.17	0.24	0.17	0.50**	−0.30
	Experience Seeking	0.05	0.06	−0.04	−0.13	−0.05
	Boredom Susceptibility	0.03	0.06	0.03	0.31	−0.24
	Total	−0.02	−0.03	−0.02	0.14	−0.12
FEE	Death	0.16	0.26	0.16	0.23	−0.27
	Body Secretions	0.02	−**0.00**	0.35	0.40*	−0.25
	Spoilage	0.15	0.09	0.02	0.30	−0.10
	Hygiene	0.17	0.08	0.16	0.40*	−0.32
	Oral rejection	0.28	0.30	0.22	0.33	−0.41*
	Total	0.18	0.14	0.17	0.37*	−0.30
FKK	Self-concept (SC)	−0.19	−0.06	−0.18	−0.38*	0.20
	Internality (I)	−0.09	0.05	0.03	−0.09	−0.05
	Powerful others (P)	0.19	0.08	0.08	0.34	−0.11
	Chance-control (C)	0.19	0.00	0.03	0.26	−0.08
	SC + I	−0.24	−0.06	−0.18	−0.34	0.16
	P + C	0.20	0.05	0.06	0.34	−0.10
	Total	−0.03	−0.08	0.09	−0.01	0.08
FSQ	Avoidance Coping	0.59***	0.68****	0.67****	0.97****	−0.77****
	Fear of Harm	0.63****	0.71****	0.73****	0.98****	−0.77****
	Total	0.60***	0.70****	0.72****	1.00****	−0.78****

(Continued)

TABLE 1 | (Continued)

Questionnaire/Scale		Fishing	Path-Choice	Touch the Enemy	FSQ	Valence spider
IE4	Internal	0.00	0.12	**0.18**	−0.14	0.01
	External	0.16	0.24	**0.10**	0.45*	−0.31

**p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.00031. Bold values indicate that the respective partial correlation was significant when controlling for Fear of Spider Questionnaire (FSQ). BDI, Beck-Depression Inventory II; TAI, Trait Anxiety; CID-S, Composite International Diagnostic Screener; SAS, Fear of Spiders Screening; RSES, Rosenberg's global Self-Esteem; SSQ, Simulator Sickness Questionnaire; PQ3, Presence Questionnaire 3; IPQ, iGroup Presence Questionnaire; BFI, Big Five Inventory; ASI, Anxiety Sensitivity Index 3; SSSV, Sensation Seeking Scales; FEE, assessment of disgust sensitivity; FKK, competence and locus of control; FSQ, Fear of Spider Questionnaire; IE4, Short Scale for the Assessment of Locus of Control.*

et al., 2014). However, our effects were rather small, and we could not detect group differences in all tasks. We suspect that this is due to difficulties arising from the free movement of participants: As we were interested in overt behavior, the intensity of participants' body movements varied greatly, which is known to have a strong effect on heart rate (e.g., Hammond and Froelicher, 1985). Likewise in the search task, participants had frequent head movements in response to the task, resulting in large fluctuations in illuminance that affects pupil size (e.g., Watson and Yellott, 2012). However, if the influence of illuminance could be controlled, pupillometry seems to be more sensitive than heart rate for measuring fear, as suggested by the larger effect sizes of pupillometry compared with heart rate in the behavioral approach task. In this study, we had 98% power to detect large effects and 14% power to detect small effects, so if physiological effects are indeed smaller, we simply need larger studies, although this is not necessary for the behavioral effects.

In contrast to our previous study (Binder and Spoormaker, 2020), in which we did not find any reliable relationship between avoidance behavior and the Beck-Depression Inventory or the scales of the Anxiety Sensitivity Index, we detected now several correlations between these variables. However, these questionnaire scales were also correlated with the FSQ, and when we controlled for this, there were no other correlations. This indicates that these traits had no direct influence on avoidance behavior but were rather related to spider phobia, fitting the positive association of specific phobia with both comorbid depression (Choy et al., 2007a; Lieb et al., 2016) and anxiety sensitivity (Olatunji and Wolitzky-Taylor, 2009). Another explanation could be that in our previous study, we included only healthy participants, which resulted in low variance in the questionnaire scales. By including spider phobic participants in this study, we increased the variance and thus improved the detection of the correlations.

We also aimed to investigate the feasibility of the procedure and its tasks, as confronting a phobic with the feared animal might be critical, especially in a fully automated setup. Although we included phobics who reported severe problems with spiders in the CIDI, all participants were able to complete the procedure without manual intervention. Even in the behavioral approach task, all participants were able to touch the spider. This is surprising considering that even after *in vivo* exposure, 10–20% of patients are unable to do so (Choy et al., 2007b). In the unstructured interview at the end of the procedure, the phobics reported that this was possible because it was not a real spider, which is in line with the moderate rating of the experienced realism in the iGroup Questionnaire. Nevertheless, they did show robust avoidance behavior and strong subjective fear. This is a key element of iVR: Although it is clearly an artificial environment, it triggers real emotions and real behavior. This is reflected in the effects of VR exposure therapy, which are a similar size to the effects of exposure therapy *in vivo* (Carl et al., 2019). Moreover, compared to *in vivo* exposure, iVR has the advantages that it is highly standardized, and the feared stimulus can be flexibly adapted to the patient's phobia without the need for maintenance and upkeep. Our results further enhance VR exposure therapy by providing multiple objective measures such as distance, choice, timing, eye gaze, body orientation, and hand movements, allowing for a holistic quantification of momentary fear levels that can be determined online and used to automatically adjust the intensity of exposure. In addition, we have demonstrated the feasibility of a fully automated iVR procedure with several degrees of exposure for patients with severe specific phobia. In this way, our findings could contribute to an efficient, fully automated, and accepted therapy for specific phobia that provides not only talk therapy but also training in real-life situations with direct active learning. No costly trained therapists are needed making it easier to scale up and offer therapy to more people (Freeman et al., 2018).

A limitation of this study is the rather small sample size. Therefore, we were only able to detect large effects and we cannot say anything about small or moderate effects. Future research should aim at larger sample sizes, especially when interested in physiological readouts. Another limitation is the restriction to female participants only, which limits the generalization to male subjects.

In summary, phobics successfully managed all tasks and showed consistent avoidance behavior across all behavioral tasks in iVR, which was also reflected in eye gaze, body orientation, and hesitation. Participants entirely without fear of spiders consistently showed no avoidance behavior across all tasks. Non-phobic participants with subthreshold moderate levels of phobic fear showed some avoidance behavior depending on the tasks, which differed in the task relevance of the spider and the degrees of freedom. Additionally, we identified subjective valence ratings of the spider as main influence on both objective avoidance behavior and subjective well-being after exposure, independent of general phobic-fear levels. Patients could benefit from this study in two ways: First, the holistic quantification of the momentary fear level allows for a more precise adjustment of the intensity of the exposure, thus improving the acceptance and efficiency of the therapy. Second, the discussed possible influences of perceived control and appearance of the feared stimulus might provide additional concepts to work on in therapy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Ethics Committee at the Faculty of Medicine at Ludwig Maximilian University of Munich. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FB and VS designed the study with support of PZ and DP. FB developed and implemented the tasks, recruited the participants, acquired, and analyzed the data. FB and VS interpreted the data. FB wrote the manuscript under supervision of VS and contribution of PZ and DP. All authors read and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnbeh.2022.827673/full#supplementary-material

Supplementary Data Sheet 1 | Supplementary tables and figures.

Supplementary Data Sheet 2 | Underlying data.

Supplementary Video 1 | Video of the Fishing task.

Supplementary Video 2 | Video of the Path-Choice task.

Supplementary Video 3 | Video of the Touch the Enemy task.

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