Review

VIRTUAL REALITY EXPOSURE THERAPY IN ANXIETY DISORDERS: A SYSTEMATIC REVIEW OF PROCESS-AND-OUTCOME STUDIES

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In recent years, virtual reality exposure therapy (VRET) has become an interesting alternative for the treatment of anxiety disorders. Research has focused on the efficacy of VRET in treating anxiety disorders: phobias, panic disorder, and posttraumatic stress disorder. In this systematic review, strict methodological criteria are used to give an overview of the controlled trials regarding the efficacy of VRET in patients with anxiety disorders. Furthermore, research into process variables such as the therapeutic alliance and cognitions and enhancement of therapy effects through cognitive enhancers is discussed. The implications for implementation into clinical practice are considered. Depression and Anxiety 27:933–944, 2010. © *2010 Wiley-Liss, Inc.*

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In the past 10 years, virtual reality exposure therapy (VRET) has become an interesting alternative for exposure in vivo in treating anxiety disorders, more specifically in treating specific phobias.[1,2] VRET is regarded as a natural extension of the systematic exposure component of behavior therapy.[3] Especially in specific phobias VRET has been found to be at least as effective as the state-of-the-art treatment exposure in vivo.[1] Although a number of studies has investigated the outcome and to a lesser extent the process of VRET, not all studies meet stringent methodological criteria and are externally valid.[4] Moreover, most of the randomized controlled trials (RCTs) within this research field have been limited to subjects with acrophobia and fear of flying. Research concerning the efficacy of VRET in other (anxiety) disorders is still in its infancy.

Quite little is known about therapeutic processes involved in VRET. Very few studies have addressed emotional processing, cognitive processes, or psychophysiology during VRET. Another important aspect, which still has been neglected in this field, is the role of the therapeutic alliance in VRET. Although the therapeutic alliance has been the most studied variable in other psychological interventions,[5] only one study explicitly addressed the role of the therapeutic alliance in VRET.[6] The first aim of this article is to provide an overview of studies into the efficacy of VRET; we limit ourselves to the discussion of studies with high methodological criteria and validity. For an overview about the technical possibilities we refer to Krijn and colleagues, who provided a solid survey of the different systems of VRET.[7] A second objective of this review is to give an overview of research that investigates mechanisms of VRET, including cognitive processes, psychophysiology, and the therapeutic alliance.

THE EFFICACY OF VRET

Although a lot of research has been published on the efficacy of VRET we will confine our discussion to the controlled studies in this field. To ensure a systematic overview, the following search strategy was applied.

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A computer-assisted search of the databases PsychInfo, Pubmed, Web of Science, and Academic Search Premier was conducted with the following search terms: "VRET" alone AND in combination with "efficacy, effectiveness, specific phobias, panic disorder, social phobia, agoraphobia, generalized anxiety disorder, obsessive compulsive disorder, posttraumatic stress disorder (PTSD), process, mechanism of change, underlying mechanism, mechanism, therapeutic process."

The search was continued by using the "snowball method." All studies retrieved were analyzed by both authors. To enhance a high quality of clinically relevant and methodologically well conducted studies, the following inclusion criteria were applied:

- Studies should focus on the efficacy or effectiveness or process of VRET.
- Only studies with at least two different conditions will be included (experimental group vs. control condition). The control group existed either of another type of intervention or a waitlist control.
- Only studies, which report original empirical findings, and those that are published in a peer-reviewed journal or proceedings will be included.
- Only articles written in English will be included.

Studies were excluded, if they:

- Assess effectiveness or efficacy of VRET in a non-clinical population, whose subjects are not suffering from an anxiety disorder at the time of the study (e.g. college students).
- Case-studies.
- Data reported based on relatively small sample size ($N \leq 10$) in the VRET condition.

The search generated 743 hits. After applying the inclusion and exclusion criteria 20 studies remained; additionally, two meta-analyses were included. See Figure 1 for an overview of the number of hits generated by the search terms. For an overview of the included studies and the main features of these studies see Table 1.

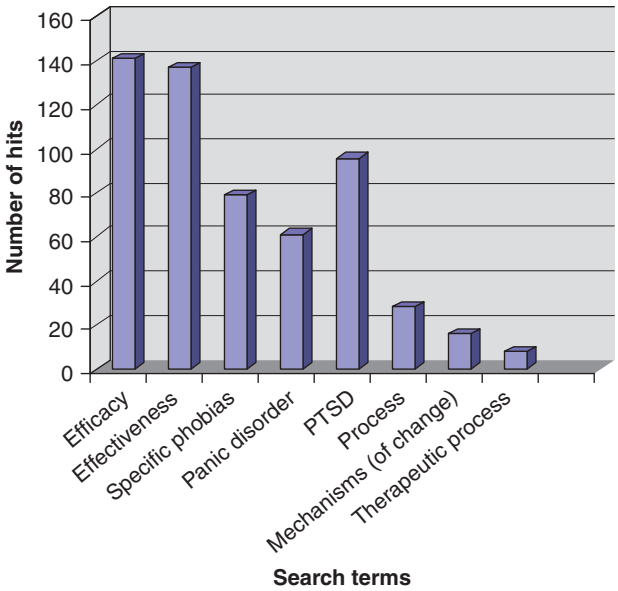

Figure 1. Search terms and generated hits. *Virtual reality exposure therapy alone generated a total of 636 hits.

SPECIFIC PHOBIAS: FEAR OF FLYING

In the first RCT on fear of flying ($n = 49$), three conditions were compared: (1) VRET, (2) standard exposure in vivo, and (3) a waiting list control group.[8,9] Each group received a total of eight treatment sessions. The first four sessions consisted of anxiety management, which was identical for the active treatment groups. The last four sessions consisted of exposure to an airplane, either in vivo or in virtual reality. VR exposure included four VR flights with visual and acoustic simulations presented by a head-mounted display (HMD) and vibration simulation presented by a low-frequency speaker built into the seat. Standard exposure sessions were held at the airport consisting of real pre-flight situations (ticketing, baggage drop-off, and sitting in a stationary airplane). After treatment, a behavioral avoidance test (BAT) was conducted consisting of a post treatment real flight. VRET and standard exposure in vivo were equally effective on the BAT and on self-report measures and significantly more effective than the control group. Treatment gains remained stable at six months and 12 months follow-up. One major limitation of this study is that both treatment conditions were combined with anxiety management training. The time spent with the therapist was identical in both conditions; however flight situations differed between groups. Unfortunately, no separate evaluation of the different treatment components took place. Research results were replicated in another series of patients ($n = 75$) with fear of flying.[10] However, also in this study anxiety management was included in the eight treatment sessions and no therapy component evaluation was done.

Mixed results were found in another RCT.[11] Here VRET (five sessions) was compared to an attention placebo group. While at post-assessment VRET was more effective than the attention placebo group on self-report measures, no significant differences were found on a BAT (post-treatment test flight). At six months follow-up, VRET was superior on only one out of the five self-report measures.

In another comparative evaluation, VRET was compared with a relaxation group.[12] Flight phobics were randomly assigned to either receive four virtual reality flights in one lengthy session or an equal amount of time in relaxation training. Fear of flying improved in both treatment groups, but several

outcome measures indicated greater effects in the VR condition than in the relaxation condition including self-ratings of fear of flying and avoidance of flying and physiological fear responses.

In a study on one-session treatment of fear of flying, a combination of cognitive behavior therapy (CBT plus VRET with or without motion simulation) was superior to CBT.[13] Results of the combination treatment were superior to results of a non-randomized control group; results of CBT alone were not superior. Motion simulation did not enhance efficacy of VRET. Results remained stable at six-month follow-up. However, group differences in self-initiated flights during the follow-up period did not reach significance. Limitations of this study include substantial difference in the time spent with the therapist: in the combined condition, subjects spent approximately 140 min with their therapist, while in the CBT conditions subjects spent only 60 min with their therapist. Time in therapy and the attention received by the therapist during this time may distort results in favor of the combined group. Another limitation is that the allocation to the control group was not randomized, which makes results difficult to interpret.

Another study evaluated the long-term effects of only one treatment session.[14] During a test flight after treatment subjects were either accompanied by a therapist or not. All subjects ($n = 30$) received one session of VRET (four successive VR flights of 18 min each). These results indicate that the attention or the presence of a therapist during a test flight did not enhance the capability of clients to fly. Results were stable at 12-months follow-up. Seventy seven percent of the whole group was able to take the graduation flight after only one treatment session; there were no differences between both conditions.

In a comparison of VRET with imaginal exposure, it was found that eight sessions of VRET were more effective than eight sessions of imaginal exposure.[15] Further, VRET plus biofeedback (feedback based on physiological monitoring) was more effective than VRET without biofeedback.[16] Finally, four sessions of VRET were compared with four sessions of CBT, and with bibliotherapy over a five-week period.[17] All subjects received a psycho-educative book about fear of flying. At the intermediate test, both VRET and CBT were superior to bibliotherapy. All participants received in addition a two-day CBT program in groups of five to eight participants, including exposure in vivo consisting of a real flight from Amsterdam to Italy. Although at the intermediate test, no differences between VRET and CBT were found, results at the post-test indicated that CBT plus group intervention was superior to VRET plus groups intervention. Unfortunately, the number of drop-outs was very high, especially in the VRET condition. However, intent to treat analyses did not show different patterns than the completers analyses. Post hoc analyses revealed that individual CBT and bibliotherapy enhanced positive cognitions about flying while VRET and the group intervention lessened negative cognitions.

SPECIFIC PHOBIAS: ACROPHOBIA

The first clinical trial on VRET with acrophobia involved a within group design.[18] Ten patients were first treated with two sessions of VRET followed by two sessions of exposure in vivo. Virtual reality exposure was found to be at least as effective as exposure in vivo on anxiety and avoidance. In a following study by the same research group, VRET and exposure in vivo were compared in a RCT.[19] To enhance the comparability of the exposure conditions, virtual environments and real life situations were identical. Subjects ($n = 33$) were randomly assigned to either three sessions of VRET or three sessions of exposure in vivo. Measures also included a BAT at post assessment. Results indicated that both treatments were equally effective and that practicing in a virtual environment did generalize to the real world as assessed with a BAT. Results were maintained at six-months follow-up.

In another study done by this group, the effectiveness of different VRET systems was investigated.[20] Subjects ($n = 37$) with acrophobia were randomly assigned to either VRET administered by a HMD, or a computer animated virtual environment (CAVE), or a waitlist control group. Subjects in the active treatment conditions received three sessions of one hour each. After the waiting period, subjects were randomly assigned to one of the active treatment conditions. Results showed no differences between the active treatment conditions on any of the measures. However, in the CAVE condition, subjects experienced more presence than in the HMD condition, but that did not influence the effectiveness of the therapy.

In a following study, the role of cognitive self-statements was investigated.[21] In a cross-over design, subjects with acrophobia ($n = 26$) were randomly assigned to either (1) two sessions of VRET followed by two sessions of VRET with cognitive self-statements or (2) two sessions of VRET with cognitive self-statements followed by VRET. Thus, all subjects received a total of four sessions. Results showed that the addition of cognitive self-statements did not enhance the effectiveness of VRET.

SOCIAL PHOBIA

While in studies done with subjects with fear of flying or acrophobia, the treatment focus is only on feared situations, in more complex phobias such as social anxiety different aspects have to be taken into account as well. In social anxiety, not only the phobic situation plays an important role but also how the subject is evaluated by others participating in the situation (e.g. giving a presentation is anxiety provoking, but also the (negative) evaluation from others causes anxiety). Given the complexity of social phobia,

TABLE 1. Overview outcome studies VRET

Study	*N*	Clinical sample	Design	Condition (*N*)	No. sessions	Primary outcome measure	Post assessment	Follow-up
Specific phobias								
Emmelkamp et al.[18]	10	Acrophobia	Within-subjects design	VRET (*N* = 10) In Vivo Exposure (*N* = 10)	2 2	AQ ATHQ	VRET = In Vivo[a]	No
Emmelkamp et al.[19]	33	Acrophobia	RCT	VRET (*N* = 17) In Vivo Exposure (*N* = 16)	3 3	BAT AQ ATHQ	VRET = In Vivo	6 months, stable
Krijn et al.[7]	37	Acrophobia	RCT	VRET: HMD (*N* = 10) VRET: CAVE (*N* = 14) WL-control (*N* = 11)	3 3	BAT AQ ATHQ	HMD = CAVE > WL[b]	6 months, stable
Krijn et al.[21]	26	Acrophobia	Crossover design	VRET+VRETCSS (*N* = 14) VRETCSS+VRET (*N* = 12)	4 4	AQ ATHQ	VRET = VRETCSS	6 months, stable
Krijn et al.[17]	59	Fear of flying	RCT	VRET (*N* = 30) CBT (*N* = 23) Bibliotherapy (*N* = 19)	4 2–4	FAS FAM	VRET = CBT VRET > Bib CBT > Bib	No
Maltby et al.[11]	45	Fear of flying	RCT	VRET (*N* = 20) Attention placebo (*N* = 23)	5 5	BAT FAS FAM FHF	VRET > APGT	6 months, results were not stable, VRET > APGT on only one measure
Mühlberger et al.[12]	30	Fear of flying	RCT	VRET (*N* = 15) Relaxation (*N* = 15)	1 1	FFS GFFQ	VRET = Relaxation	No
Mühlberger et al.[13]	45	Fear of flying	RCT	VRCBT+MS (*N* = 13) VRCBT−MS (*N* = 13) CBT (*N* = 11) WL-control (10)	1 1 1	BAT FFS GFFQ	VRCBT > CBT, MS = no difference > WL	6 months, stable for VRCBT
Mühlberger et al.[14]	30	Fear of flying	RCT	Flight 1 year follow-up alone (*N* = 15) Flight 1 year follow-up with therapist (*N* = 15)	1 1	BAT FFS GFFQ	VRET alone = VRET acc	12 months, stable
Rothbaum et al.[8,9]	49	Fear of flying	RCT	VRET (*N* = 15) standard exposure (*N* = 15) WL-control (*N* = 15)	8 8	BAT QATF FFI	VRET = SE, VRET > WL, SE > WL	6 and 12 months, stable
Rothbaum et al.[10]	75	Fear of flying	RCT	VRET (*N* = 32) standard exposure (*N* = 34) WL-control (*N* = 25)	8 8	BAT QATF FFI	VRET = SE, VRET > WL, SE > WL	6 – 12 months, stable
Wiederhold and Wiederhold[15]	30	Fear of flying	RCT	VRET (*N* = 10)[c] VRET+biofeedback (*N* = 10)[c] Imaginal exposure (*N* = 10)[c]	8 8 8	EEG BWM RR SR HR ST	VRET+biofeedback > VRET > IET	3 years, stable

Social phobia								
Klinger et al.[22]	36	Social phobia	RCT	Individual VRET ($N = 18$) Groups CBT ($N = 18$)	12	LSAS	VRET = CBT	No
Wallach et al.[24]	88	Fear of public speaking	RCT	VRCBT ($N = 28$) CBT ($N = 30$) WL ($N = 30$)	12 12	BAT LSAS SSPS FNE	VRCBT = CBT > WL	Not yet; still in progress
Panic disorder								
Botella et al.[28]	37	Panic disorder	RCT	VRET ($N = 12$) In vivo exposure ($N = 12$) WL-control ($N = 13$)	9 9	PDSS ASI FQ	VRET = In vivo exposure > WL	12 month, stable
Choi et al.[26]	40	Panic disorder	RCT	Group experiential cognitive therapy (ExCT; $N = 20$) Panic control program (PCP; $N = 20$)	4 12	PBQ ACQ BSQ	ExCT = PCP	6 months, stable on main outcome; medication discontinuation higher in the PCP
Penate et al.[29]	27	Panic disorder	Matched between subjects design	VRET ($N = 15$) CBT ($N = 13$) matched with an antidepressant	11 11	AQ (1) ACQ BSQ BAT	VRET = CBT	3 months, stable
Pitti et al.[30]	28	Panic disorder	Matched between subjects design	VRET ($N = 18$) CBT ($N = 9$) matched with an antidepressant	11 11	AI ACQ BSQ	VRET = CBT	
PTSD								
Ready et al.[32]	14	PTSD	Open trial	VRET ($N = 14$)	Flexible up to 20 sessions	CAPS IES	Significant pre-post changes	6 months, stable and further symptom reduction
Difede et al.[31]	21	PTSD	Quasi-experimental design	VRET ($N = 13$) WL-control ($N = 8$)	Flexible up to 14 sessions	CAPS BDI	VRET > WL	No

[a]Treatment A is equally effective as treatment B.
[b]Treatment A is superior to treatment B.
[c]*N* per condition estimated; VRCBT, virtual reality cognitive behavior therapy; MS, motion simulation; APGT, attention placebo groups therapy; WL-control, waiting list control; FU, follow-up; VRETCSS, virtual reality exposure therapy plus cognitive self-statements; AQ, Acrophobia Questionnaire; ATHQ, attitude towards Heights Questionnaire; BAT, behavioral avoidance test; FAS, Flight Anxiety Situations Questionnaire; FAM, Flight Anxiety Modality Questionnaire; FHF, flying history form; FFS, Fear of Flying Scale; GFFQ, General Fear of Flying Questionnaire; QATF, Questionnaire Attitude Towards Flying; LSAS, Liebowitz Social Anxiety Scale; SSPS, Self-Statement Questionnaire during Public Speaking; FNE, fear of negative evaluation; PDSS, Panic Disorder Severity Scale; ASI, Anxiety Sensitivity Index; FQ, Fear Questionnaire (Agoraphobia Subscale); PBQ, Panic Belief Questionnaire; ACQ, Agoraphobic Cognitions Questionnaire; BSQ, Bodily Sensation Questionnaire; AQ (1), Agoraphobia Questionnaire; AI, Agoraphobia Index; CAPS, Clinician Administered Posttraumatic Stress Disorder Scale; IES, Impact of Event Scale; BDI, Beck Depression Inventory; EEG, electroencephalograph; BWM, brain wave measurements; RR, respiration rate; SR, skin resistance; HR, heart rate; ST, skin temperature.

treatment often consists of group therapy, which in turn might be too aversive for socially anxious patients.

A study investigating the effects of VRET for social phobia compared individual VRET to group CBT.[22] All subjects ($n = 36$) received 12 sessions of therapy. Patients were not randomized, but allocation to condition was based on matching for age and gender. No BAT was included so results are based on self-report measures only. Although results indicated that differences in outcome between the two treatment groups were trivial, no real control condition for the effect of time (e.g. waitlist control) was added, which makes the clinical effects achieved difficult to evaluate. In addition, a possible confound is the comparison of an individual treatment (VRET) with a group treatment. Especially in the treatment of social phobia where social contact in the context of participation in a group can be interpreted as exposure in vivo to a feared stimulus, group treatment may confound the effects of CBT per se.

One subcategory of social anxiety is fear of public speaking. Often, the state-of-the-art treatment (CBT including exposure in vivo) is quite difficult to organize and too aversive for the patient. In a first open trial ($n = 10$) four sessions VRET were combined with four sessions of anxiety management training.[23] Results indicated significant improvement on specific fear of public speaking measures. In the first RCT with a clinical sample of subjects ($n = 88$) with fear of public speaking, the following three conditions were compared: CBT vs. CBT plus VRET vs. a waitlist control group.[24] Both treatment protocols consisted of cognitive and behavioral components (respectively e.g. working with the cognitive model of social phobia and a presentation of the cognitive model in virtual reality or in imagination). All subjects received 12 individual therapy sessions. Results indicated that CBT plus VRET was equally effective as CBT and both were superior to the control condition on anxiety measures and on a BAT. Although CBT was as effective as CBT plus VRET, twice as many subjects dropped out of CBT (significant difference) and therefore the originally planned randomized design was changed to a weighted assignment. This non-random assignment is a major limitation of this study. However, conclusions are quite firm concerning generalization to the real world and the much lower drop out rates in the CBT plus VRET group are promising.

PANIC DISORDER

In a more complex anxiety disorder such as panic disorder with agoraphobia, few RCTs have been reported. Treatment has to focus on panic as well as on agoraphobic avoidance behavior.[25] Exposure to agoraphobic avoidance behavior consists of exposing individuals to a variety of situations which they fear—this can be easily done in virtual environments.

Four clinical trials, which investigated the effects of VRET in subjects with panic disorder, have been published. The first study compared group experiential cognitive therapy (including VRET) to a panic control program in a between subjects design.[26] Subjects ($n = 40$) received either four sessions of experiential cognitive therapy (consisting of psycho-education, relaxation training, interoceptive exposure, and VR exposure) or 12 sessions of a panic control program (based on Craske and Barlow).[27] All treatments were given in groups except for the VR exposure component. At post-assessment both treatment conditions were equally effective. However, results were not maintained at six-months follow-up, where the panic control program obtained a higher end-state functioning than the other treatment group. A major limitation of this study is that both treatment conditions received an unequal amount of treatment sessions. Interestingly, the experiential cognitive therapy achieved at post assessment the same results with less therapy sessions than the panic control program. This aspect and the multi component treatment (components were not evaluated separately) makes generalization difficult. Unfortunately, no BAT was included to control for generalization to the real world.

In a RCT done by Botella, Garcia-Palacios, Villa, Banos, Quero, Alcaniz et al. stricter methodological criteria were applied.[28] Subjects ($n = 37$) were randomly assigned to either nine treatment sessions of CBT plus VRET, or nine sessions of CBT plus exposure in vivo, or to a waiting list control condition. Results indicated that there were no differences in effectiveness between the two active treatment conditions. Both active treatment conditions were superior to waitlist controls. The results remained stable at 12-months follow-up. Also in this study no BAT was included.

In the third clinical trial done by Penate, Pitti, Bethencourt, de la Fuente, and Gracia,[29] a matched between subjects design was used to compare VRET to CBT in subjects with panic disorder. Subjects ($n = 28$) received either 11 sessions of CBT or of a combined treatment of CBT and VR. CBT included exposure in vivo. Additionally, all subjects received antidepressant medication. A BAT was conducted at post assessment to investigate generalization. CBT and the combined VRET-CBT program were found to be equally effective at post-test, and at three-months follow-up. In a RCT done by the same research group, 27 subjects with a diagnosis of panic disorder and agoraphobia received either CBT (including exposure in vivo) or a combination of CBT and VRET.[30] All subjects received antidepressant medication. There was an overlap of subjects in the medication condition in the studies from Penate et al. and Pitti et al. (personal communication, 02–20–2010). No significant differences between groups were reported. However, a slight trend in favor of the combined condition was found. Results of these studies are difficult to interpret

because of the overlap in subjects and because in the combined condition, patients also received a number of exposure in vivo sessions.

In summary, the results of pure VRET have hardly been investigated in panic disorder and agoraphobia. Only Botella et al.[28] compared VRET and in vivo exposure directly and found both components equally effective.

PTSD

To date, only one comparative treatment outcome study was published on VRET in PTSD. In a quasi-experimental (matched) design VRET was compared to a waitlist control group.[31] Subjects ($n = 21$) underwent a flexible amount of exposure sessions, with a maximum of 14 sessions. At post assessment, the VRET group improved significantly on specific PTSD measures, whereas the control group did not: this difference between groups was significant. Thus, preliminary results indicate that VRET could be a useful intervention in subjects with PTSD at least in some cases. These data are also supported in an open trial study.[32,33] In this study veterans diagnosed with PTSD underwent VRET. Subjects improved significantly on specific PTSD measures, with stable results at follow-up three and six months later. Possible problems in patients with PTSD are that traumas are too idiosyncratic to be treated with standard virtual environments and that it often will be impossible to create virtual environments that are realistic (e.g. child abuse and rape).

META-ANALYSES

Two meta-analyses have been reported concerning the effectiveness of VRET in anxiety disorders.[1,2] In both studies VRET was found to be equally effective or superior to a variety of control groups. In one meta-analysis,[1] 13 studies ($n = 397$) were included. Studies were excluded that involved case reports, multiple components of treatment conditions, and unequal amount of treatment sessions in the treatments compared. *Between* group effect sizes varied from 0.85 until 1.67 (Cohen's *d:* small: 0.2; medium: 0.5; and large: 0.8). There was a small effect size ($d = 0.35$) favoring VRET over exposure in vivo. Generally, effect sizes of VRET were large to very large, but most of the studies involved specific phobias. In the other meta-analysis less strict criteria were applied and 21 studies ($n = 300$) were included in the analysis.[2] The average *within* group effect sizes varied from 0.87 until 1.79: PTSD = 0.87; social phobia = 0.96; acrophobia = 0.93; panic disorder with agoraphobia = 1.97; fear of flying = 1.59. Unfortunately, also case reports were included, which makes comparability with RCTs rather difficult, especially given the different anxiety disorders investigated, and the different amount of treatment sessions in the studies compared, which was not controlled for in the analyses.

CONCLUDING REMARKS

Applying strict methodological criteria concerning research into the effects of treatment of anxiety disorders with virtual reality exposure, this review gives a more sobering look on the state-of-the-art of research in this area and compared to earlier reviews (e.g.[7]). Although the two meta-analyses reported report promising effect sizes for VRET in general[2] and in comparison with exposure in vivo,[1] generalization across anxiety disorders is hardly possible. Only in two specific phobias (fear of flying and acrophobia[8–11,13–15,17–21]) more or less systematic research has been done to be able to state that VRET indeed is effective in comparison with the state-of-the-art CBT treatment and controlled for the effect of time. Results of VRET on behavioral measures at post-treatment are impressive, suggesting that the results of VRET indeed generalize to the real world. Given the high rate of treatment refusal and high drop-out rates of exposure in vivo, results of the studies discussed here suggest that treatment refusal and drop-out rates[34,35] may be lower in a treatment protocol using VR for exposure to agoraphobic situations.[28] With respect to other phobias and PTSD hardly any comparative outcome study has been reported, which make any conclusion with respect to clinical relevance of VRET for these disorders premature. Results concerning the treatment of panic disorder are promising, but definite conclusions are precluded since the effects of the VRET component in the package cannot be established in most of these studies.

PROCESS OF VRET

Although VRET is regarded as a natural extension of the systematic exposure component of (cognitive) behavior therapy,[3] to date hardly any research has examined the underlying mechanisms of change in VRET. According to the emotional processing theory of Foa and Kozak, two conditions within therapy sessions have to be met for successful emotional processing.[36,37] The fear structure has to be activated and information incompatible with this existing structure has to be presented and incorporated. In this section, research concerning cognitive, physiological, or other therapeutic variables associated with VRET will be discussed.

COGNITIVE MECHANISMS IN VRET

To analyze cognitive mechanisms during VRET different approaches have been used, including automatic processing of threatening stimuli,[38,39] and cognitive change as assessed by perceived self-efficacy and self-statements.[6,21]

The first study investigating automatic processing during VRET was done with subjects ($n = 28$) suffering from arachnophobia.[38] Subjects received an exposure-based virtual reality treatment consisting of five

sessions of 60 min weekly. Pre- and post-treatment subjects were assessed with an emotional Stroop task. The Stroop task was done with a series of color-filtered pictures (each category consisted of eight pictures) and subjects had to push the button with the corresponding color as quickly as possible. For positive emotional content a rabbit was chosen, for the neutral emotional content a cow was chosen, and a spider was chosen for the negative emotional content. Results showed a significant difference between pre- and post-treatment, indicating that threat interference reduced significantly while the response time for positive interference did not. The authors conclude tentatively that treatment had a significant impact on information processing.

In another publication based on the same subjects,[39] the perceived self-efficacy and threat-related beliefs of subjects were analyzed. Results indicated that general improvement on self-report measures was only significantly predicted by changes in self-efficacy, but changes in threat-related beliefs were nonpredictive for general improvement. A reverse pattern was observed for improvement on the BAT. Changes in dysfunctional threat-related beliefs were the only significant predictor of an increased performance on the BAT. Thus, perceived self-efficacy and threat-related beliefs play an important but distinct role during VRET.

It is of some interest to analyze self-efficacy also in context of other cognitive variables as for example positive and negative thoughts one has about him or herself. Positive self-statements can also be interpreted in a sense of coping mastery while negative self-statements may promote avoidance behavior.[40] In a process study involving subjects with fear of flying ($n = 14$) or acrophobia ($n = 20$) self-efficacy and negative self-statements were assessed over the course of treatment.[6] Subjects received four weekly exposure sessions each of 50 min in a virtual environment. Although cognitions were not directly addressed during VRET, results indicated that self-statements changed significantly during VRET: four sessions of VRET led to a significant reduction in anxiety, enhanced self-efficacy, and a decrease in negative self-statements.

The steady increase in self-efficacy over the course of four VRET sessions is in line with a study in which it was found that VRET led to a linear increase in self-efficacy in subjects ($n = 26$) with acrophobia..[21] In this study subjects were randomly assigned to two sessions of VRET followed by two sessions of VRET plus coping self-statements, or the other way around. As discussed already above, results indicated that the addition of coping self-statements did not influence the effectiveness of treatment. Given the cross-over design used no conclusion can be drawn on the change of cognitions during VRET as stand-alone treatment.

In summary, results into cognitive change during VRET are still in its infancy. The few studies addressing cognitions during the process of VRET use a variety of approaches, which shed some light on cognitive processes, but are not yet conclusive. Although there is some evidence that VRET may lead to change on implicit measures,[38] it is still questionable whether the Stroop task used provides a reliable indication of automatic processing.[41,42] More promising results were revealed with respect to changes in self-efficacy and self-statements over the course of VRET.[6,17] There is a clear need for process research focusing on designs to analyze possible cognitive mediators and moderators and to determine temporal precedence in mechanisms of cognitive change in VRET.

THERAPEUTIC ALLIANCE AND EXPECTANCY OF THERAPEUTIC GAINS

A central process aspect concerning therapy outcome is the therapeutic alliance between therapist and client. Since Freud's[43] emphasis on the role of the client–therapist relationship, the importance of the relationship between client and therapist is being recognized within nearly all schools of psychotherapy. Because of its modest but stable ability to predict treatment outcome, the therapeutic alliance has become one of the most studied process variables in psychotherapy research.[44] Although the therapeutic alliance is an established predictor of psychotherapy outcome, alliance research in technology-based psychological treatment has been neglected.[45]

In a recent study the mediating role of the therapeutic alliance was investigated in subjects with fear of flying ($n = 14$) or acrophobia ($n = 20$).[6] One of the aims of that study was to examine whether the quality of the therapeutic alliance predicted successful outcome in VRET in terms of anxiety reduction. Results indicated that the quality of the therapeutic alliance as assessed with the Working Alliance Inventory[46] was positively related to treatment outcome in the fear of flying group but not in the acrophobia group. The discrepancy with respect to the predictive value of the therapeutic relationship between the two groups might be related to differences in challenges within the exposure sessions, which differed for the two groups. In the fear of flying patients exposure was standardized for all patients eliciting moderate anxiety, while exposure in the patients with acrophobia was more challenging in that therapists pushed the patient more to do more difficult exercises. There is a clear need for further studies into the mediating role of the therapeutic relationship in VRET.

Further, there is some evidence that positive expectancy of patients with respect to outcome of VRET may enhance improvement. In a study with subjects with fear of flying ($n = 72$) higher expectancies for treatment outcome of VRET led to stronger symptom reduction on self-report measures.[47]

In summary, research into the role of expectancy of therapeutic gains and the therapeutic alliance in VRET is still in its infancy. So far, only two studies

investigating different therapeutic mechanisms (i.e. the therapeutic alliance and treatment outcome expectancies) have been reported and give only first notions in which direction future research should develop.

PSYCHOPHYSIOLOGY IN THE PROCESS OF VRET

More extensive research has been done with psychophysiological measures into the process of VRET. Different physiological measures as heart rate, heart rate variability, or galvanic skin conductance have been used to analyze physiological arousal and habituation processes in VRET.

A study investigating whether during VRET a different motivational system is activated than during exposure in vivo was done with 20 subjects categorized into high- and low-anxious group.[48] The behavioral activation system (BAS) and the behavioral inhibition system (BIS) are considered differentially responsible for treatment effects with exposure in vivo versus VRET. Monitoring anxiety by different physiological measures (heart rate, which reflects activity of BAS) and skin conductance (which reflects activity of the BIS) may help to determine whether the same processes underlie virtual exposure and exposure in vivo. Results indicated possible underlying physiological differences between the process of VRET and in vivo exposure. Selective activity of BIS as assessed with skin conductance was registered during VRET but no activity of BAS (changes in heart rate) was observed. Although these differences were found between in vivo exposure and VRET, results have to be interpreted with caution given that heart rate did not distinguish exposure from baseline in both groups, while large effect sizes were found for skin conductance.

The results of the above-mentioned study[48] corroborate earlier findings in a small study.[49] In this study nonphobic subjects ($n = 9$) were immersed in agoraphobic environments to investigate the pattern of change during exposure to virtual environments. Heart rate and skin conductance were registered during exposure time to four different virtual environments. Results indicated no significant changes in heart rate during exposure to virtual environments. These results have to be interpreted with caution since in such a small sample size one outlier can distort results. Additionally, skin conductance is very sensitive to bodily movements.

Heart rate was also found not to discriminate in a comparison of exposure to a virtual flight between phobic ($n = 33$) and nonphobic subjects ($n = 22$).[16] Also here significant differences between groups were found on skin resistance. Whether the differences between the groups found on skin resistance can be attributed to a VRET specific arousal in the phobic group as Wilhelm et al. propose cannot be concluded. Stricter methodological criteria (e.g. controlling for body movements) should be applied to investigate whether specific physiological arousal is associated with VRET. Further, the same subjects should be exposed to different exposure situations (VRET versus in vivo).

In a quasi-experimental design, a comparison was made between high-anxious subjects ($n = 15$; fearful of tunnels) and matched controls ($n = 15$) on physiological measures during VRET.[50] Subjects highly fearful of tunnels underwent exposure to three different virtual environments, varying in degree of anxiety provocation. Results indicated differences in heart rate only in the high-anxious group for the most anxiety evoking virtual environment, but not for the other environments. Further, no significant results were found on skin conductance. Thus, physiological reactions (heart rate) varied between virtual environments only in the high-anxious group, but not in matched controls, thus results are not in line with the results of earlier research,[16,48,49] in which a reverse pattern was found.

In studies by Côté and Bouchard[38,39] physiological reactions were observed on heart rate variability (HRV). Results indicated that the cardiac response measured with HRV was the best predictor of change in behavioral avoidance. A significant decrease in interbeat intervals was found when subjects were confronted to exposure situations,[38] indicating higher anxiety. Additionally, it was found that the cardiac response measured by HRV was best predicted by changes in perceived self-efficacy and dysfunctional beliefs.[39]

Firm conclusions about a pattern of physiological arousal during VRET cannot be drawn since no coherent pattern was found in the various studies discussed. Overall in none of the studies, consistent support was found for the emotional processing theory as indicated by changes in heart rate. More support was found for changes in skin conductance during VRET,[16,48,49] but this was not corroborated in another study;[50] all three studies, which found support, lacked sufficient statistical power. Studies with more sophisticated research designs, making a direct comparison between VRET and exposure in vivo while keeping all other variables constant, would be a valuable contribution.

ENHANCEMENT OF THERAPY EFFECTS THROUGH COGNITIVE ENHANCERS

Another increasingly important area of research concerns the enhancement of extinction processes during (virtual) exposure therapy. Extinction can be described as a form of learning, indicated by a decline in frequency and magnitude of the anxious response.[51] Experimental animal research has revealed that cognitive enhancers can augment the process of exposure[52] and therefore be a valuable contribution in future exposure-based treatments. A few studies with healthy humans[53,54] and clinical samples have supported the

notion that pharmacological agents can enhance exposure treatment[55] (for a review see[56]).

In a first study combining VRET with a cognitive enhancer subjects ($n = 28$) with acrophobia underwent VRET combined with D-cycloserine (DCS) or VRET combined with placebo.[57] In this double blind RCT, subjects were treated with two sessions of VRET. Single doses of placebo or DCS were administered before each exposure treatment. Subjects were assessed one week after treatment termination and three months after treatment termination. Results indicated that VRET plus DCS resulted in significantly larger reduction of acrophobia on all outcome measures than VRET plus placebo. The results remained stable at three months follow-up. Thus, there is some support that emotional learning during VRET can be augmented using cognitive enhancers. However, different doses of DCS were administered (50 or 500 mg), but no differences between doses were found for the primary outcome measures of acrophobia, which makes results difficult to interpret.

CONCLUDING REMARKS

This systematic review gives a sobering look on the current status of research in this field. Only in fear of flying and acrophobia is there considerable evidence that VRET indeed is effective. In more complex anxiety disorders as panic disorder and social phobia, which form the core clinical groups, first results of VRET are promising,[24,28] but more and better controlled studies are needed before the status of empirically supported treatment is reached. More severe cases of panic disorder with agoraphobia and social phobia are often not reached with existing treatments. Such patients are too scared to come into treatment because they have to leave their "safe/secure zone/circle" for that. To better reach this core clinical group, a future aim of research could be to investigate whether initial sessions can be conducted at home via an Internet port, where patients can login and start first treatment sessions in virtual reality.

In the field of treatment of PTSD until now, only two open studies support the notion that patients suffering from PTSD are improving with VRET.[31,32] But the question remains in how far PTSD can be successfully treated with virtual reality. Treatment for PTSD with virtual reality seems possible and realistic for veterans who have been traumatized in more or less comparable (war) situations. Other traumatic events/incidents are often too idiosyncratic to be rebuild in virtual environments. The treatment of PTSD with VRET in veterans can be very relevant, though, given that stereotype virtual environments for war situations can be used. Other traumatic incidents might be easier and better treated with other state-of–the-art treatments for PTSD.

A general remark is that in outcome research of VRET often multiple components are mixed in treatment protocols. First, these combined treatments are not always based on the state-of-the-art treatment for these specific disorders, which on its own makes studies on the efficacy of VRET difficult to interpret. Further, given that virtual reality exposure is often combined with other techniques, dismantling research methodology is needed to separate the contribution of the various components. Finally, a last remark on studies in this area is that often no BAT is included, in which case conclusions about generalization to real life cannot be made; generalization to the real world remains of course the ultimate measure for this treatment form.

Process studies could shed more light on mediating variables of the outcome of VRET. There is a clear need of studies investigating the cognitive and physiological processes presumed to underlie VRET. Further, research into the role of the therapeutic alliance during VRET is scarce. Research into another technology-based treatment (internet-based treatment) for post-traumatic stress suggests that such technology does not have to interfere with treatment outcome. For example, when patients did not see the therapist at all face-to-face in an internet treatment, a substantial correlation was found between the quality of the therapeutic alliance as assessed with the Working Alliance Inventory[46] and treatment outcome. Thus, there were no indications that technology-based psychological treatment interfered with the therapeutic process.[58]

Another valuable contribution that is possible through sophisticated use of VRET is research into understanding contributing factors of specific disorders. In a review of the triggers of acrophobic behavior it was concluded that motion combined with height rather than height on its own triggers phobic responses.[59] In this sense VRET can help in the future understanding treatment processes but also processes related to fear itself.

In summary, it would be a valuable addition when research into VRET would not only focus on outcome but also on the underlying processes. Understanding the processes would help implementing VRET into clinical practice given that treatment outcome would be better predictable.

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