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**Review Article** 

# Attention allocation in OCD: A systematic review and meta-analysis of eye-tracking-based research



### Dana Basel, Hadar Hallel, Reuven Dar, Amit Lazarov\*

School of Psychological Sciences, Tel Aviv University, Tel Aviv 69978, Israel

ARTICLE INFO	ABSTRACT
Keywords: Attention allocation Eye-tracking Free-viewing Obsessive-compulsive disorder Systematic review meta-analysis	Introduction: Cognitive models of obsessive-compulsive disorder (OCD) implicate heightened attention allocation to stimuli related to one's obsessions in the disorder. Recently, to overcome several limitations of reaction time- based measures, eye-tracking methodology has been increasingly used in attentional research. <i>Methods</i> : A meta-analysis of studies examining attention allocation towards OCD-related vs. neutral stimuli, using eye-tracking methodology and a group-comparison design, was conducted conforming to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. Separate meta-analyses were performed for attentional vigilance (both latency and location of first fixations) and maintenance (total dwell time and total fixation count, conjointly). Each meta-analysis was conducted twice – once including all studies (main analysis) and once only including studies using the free-viewing paradigm (secondary analysis). <i>Results</i> : The systematic search yielded a total of nine studies. Of those, eight provided the needed data to be included in the meta-analysis. No evidence emerged for vigilance via latency to first fixation. Vigilance reflected via first fixation location emerged in the main analysis, but not in the secondary one. Evidence for attentional maintenance was found only when analyzing free-viewing studies exclusively (the secondary analysis). <i>Limitations</i> : To increase the accuracy of the research question, correlational studies were excluded, resulting in a small number of available studies. <i>Conclusions</i> : OCD may be characterized by vigilance, but mainly in tasks entailing specific demands and/or goals. Conversely, attentional maintenance may be evident only when using tasks that pose no requirements or de- mands for participants.

#### 1. Introduction

Obsessive Compulsive Disorder (OCD) is a chronic and debilitating disorder affecting about 2-to-3 % of the population (Ruscio et al., 2010), characterized by obsessions and/or compulsions. *Obsessions* are recurrent and persistent thoughts, urges, images, or impulses that are experienced by the individual as intrusive and unwanted, causing marked anxiety or distress. *Compulsions* are repetitive behaviors or mental acts the individual feels driven to perform in response to an obsession, or according to rules that must be acted upon rigidly (American Psychiatric Association, 2013). Obsessions and compulsions are extremely time consuming, interfering significantly with occupational and academic functioning, as well as with social activities or relationships, impairing daily functioning and reducing quality of life (Eisen et al., 2006; Valderhaug and Ivarsson, 2005).

Cognitive models of OCD implicate misinterpretation of normal and commonly-occurring "intrusive" thoughts in the etiology and maintenance of the disorder (Salkovskis et al., 1999; Salkovskis et al., 1998). According to these models, a benign intrusive thought may become an obsession when the individual interprets the occurrence of the thought, or its content, as signaling personal responsibility for causing or preventing harm to oneself and/or others (Pleva and Wade, 2006; Rachman, 1993; Salkovskis, 1985; Salkovskis et al., 1995; Salkovskis et al., 2000). These negative interpretations, in turn, lead the person with OCD to allocate heightened attentional resources to environmental cues related to their obsessions (Cohen et al., 2003). For example, if an individual with OCD interprets the occurrence or the content of a (benign) thought/worry/image of their child being infected and becoming seriously ill as signaling their responsibility for causing ("I could infect my child and make him very sick") or preventing this from happening ("I

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<sup>\*</sup> Corresponding author at: School of Psychological Sciences, Tel Aviv University, Tel Aviv 69978, Israel.

*E-mail addresses:* danabasel@mail.tau.ac.il (D. Basel), hadarhallel@mail.tau.ac.il (H. Hallel), ruvidar@tauex.tau.ac.il (R. Dar), amitlaza@tauex.tau.ac.il (A. Lazarov).

must be sure my hands are clean so not to infect my child"), then this otherwise benign thought/worry/image would increase distress and anxiety, also resulting in increased attention allocation to contamination-related signs in one's environment (e.g., a dirty sink). Theoretically, this heightened attention allocation can manifest in attentional vigilance - easier or faster detection of these cues in the environment; and/or in attentional maintenance - goal-directed sustained attention to these cues (Cludius et al., 2019; Corbetta and Shulman, 2002). To use the previous example, an individual with contamination-related obsessions may more easily or rapidly detect a dirty plate within an array of clean dishes, reflecting attentional vigilance, and/or may maintain his attention on this plate, once detected, for a longer time, reflecting attentional maintenance. Importantly, as exemplified above, these two biases are not mutually exclusive and may operate conjointly (Lazarov et al., 2019). Thus, a patient with OCD may display facilitated threat detection, followed by difficulty to disengage attention once threat has been detected.

Early studies examining attentional biases in OCD used reaction time (RT)-based tasks and measures, such as the emotional Stroop task (Williams et al., 1996) or the modified dot-probe paradigm (MacLeod et al., 1986), in which attention bias is inferred from facilitated or impaired task performance (i.e. changes in RT) due to the presence of OCD-related threat stimuli - stimuli presumed to evoke obsessionrelated anxiety or discomfort (e.g., a picture of a key lying on the grass is presumed to provoke OCD checking-related symptoms, while a picture of a dirty toilet is assumed to provoke OCD contaminationrelated symptoms; Mataix-Cols et al., 2009; Simon et al., 2012). For example, in the dot-probe task (MacLeod et al., 1986), on each trial of the task an OCD-related threatening stimulus (pictures or words) is presented simultaneously with a neutral stimulus. Following stimuli presentation, a small probe appears at the location of one of these previously presented stimuli, with equal probability to appear in each location. Participants are asked to indicate, as quickly as possible, which probe of two different variants (e.g., "X" or "M") appeared. A threatrelated bias is assumed to manifest when participants are faster to respond to probes that appear in the location of the threat stimulus, rather than the neutral one (e.g., Dalgleish et al., 2001; Bardeen and Orcutt, 2011). These early RT-based studies have yielded some encouraging results, showing evidence for increased attention allocation to OCD-related stimuli in OCD (e.g., Amir et al., 2009; Foa et al., 1993; Rao et al., 2010; Tata et al., 1996). However, other studies found no differences in attentional allocation between participants with OCD and non-OCD controls (e.g., (Harkness et al., 2009; Kampman et al., 2002; Kyrios and Iob, 1998; Moritz et al., 2004; Van den Heuvel et al., 2005)). A potential reason for this discrepancy in results may be related to methodological differences between studies, which used different tasks (e.g., Dot-probe or emotional Stroop tasks; Amir et al., 2009; Harkness et al., 2009; Moritz et al., 2004; Rao et al., 2010;), and different participant recruitment strategies (e.g., participants with high vs. low levels of OC symptoms or clinical OCD patients vs. healthy controls; Amir et al., 2009; Rao et al., 2010).

In recent years, eye-tracking methodology – a non-invasive method which samples and records gaze data at different rates (ranging from 60 to 2000 Hz) – has been increasingly used to examine attentional processes and biases in psychopathology (e.g., Lazarov et al., 2016; Lazarov et al., 2018; Wieser et al., 2009). In eye-tracking, all facets of eye-data (e. g., fixations, saccades) are recorded, and then interpreted to characterize different attentional patterns. The free-viewing paradigm, one of the most widely used eye-tracking paradigms in research on visual attention allocation, can help illustrate this process. In this paradigm, participants are asked to freely view different stimuli, usually of different valences (e.g., happy vs. sad faces; threatening vs. neutral pictures), without any specific requirements or demands, while their gaze being continuously recorded. Facilitated threat detection, or *threat vigilance* (i.e., the ease or speed in which threat is detected), is determined by the location and/or the latency of the initial eye movements occurring immediately after stimulus onset, namely, first fixations. A greater proportion of first fixations on threat compared with neutral stimuli, or shorter latencies to first fixate on threat compared with neutral stimuli, are considered evidence of facilitated threat detection (Waechter et al., 2014). Sustained attention to threat, also termed attentional maintenance, refers to the degree to which attention is held by a threatening stimulus, once detected, due to difficulty in diverting one's attention away from it. Sustained attention is usually indicated by the total duration of all fixations (i.e., total dwell time) or the number of fixations (i.e., total fixation count) made on threat vs. neutral stimuli during stimulus presentation.

Eye-tracking methodology has several noticeable advantages in exploring visual attention allocation. First, by continuously sampling gaze data it offers an almost instantaneous measure of attention deployment, greatly improving the ability to delineate the time course of attention allocation, and to discern the different components of the attentional process (e.g., vigilance, sustained attention). Second, as no motor responses are needed to assess attention processes, using eyetracking minimizes the potentially confounding motor element, especially in free-viewing paradigms (Armstrong and Olatunji, 2012; Lazarov et al., 2016; Lazarov et al., 2021; Lazarov et al., 2019). Third, using eve-tracking enhances the efficacy of research as the different attentional components can be assessed within a single trial (e.g., vigilance, sustained attention), while also potentially providing different indices for single components (e.g., vigilance can be explored using both the location of and latency to first fixations, see measures below). Finally, eye-tracking-based measures possess adequate psychometric properties, including good internal consistency and high test-retest reliability (Chong and Meyer, 2021; In-Albon et al., 2010; Lazarov et al., 2016; Lazarov et al., 2021; Lazarov et al., 2018; Lazarov et al., 2019; Sears et al., 2019; Skinner et al., 2018; Waechter et al., 2014), which is critical for trusting emergent findings (Rodebaugh et al., 2016; Spiller et al., 2020).1

Taking into account the advantages of eye-tracking methodology in exploring visual attention allocation, the current study aimed at elucidating the specific attentional features, and their gaze-related manifestation, which may characterize individuals with OCD, also exploring the relation between these features and the different attentional eyetracking tasks used in research. This, in turn, may suggest novel targets for therapeutic interventions, especially for attention bias modification (ABM) procedures, as past ABM efforts in OCD (which, to date, only include RT-based studies) mostly showed low clinical efficacy (e.g., Habedank et al., 2017; Najmi and Amir, 2010; Rouel and Smith, 2018). Specifically, a systematic search was performed to locate all studies comparing OCD and control participants on eye-tracking-based indices of attention allocation to OCD-related and neutral stimuli, including facilitated threat detection (i.e., vigilance) and sustained attention (i.e., attentional maintenance). Vigilance was assessed by examining both latency to and location of first fixation, as these reflect different aspects of attentional vigilance (Clauss et al., 2022; Lazarov et al., 2019), with the first addressing the speed in which a cue is detected, and the latter the frequency of cue detection. Hence, it is possible for attention vigilance to manifest in one but not the other. Maintenance was assessed considering total dwell time and total fixation count conjointly, as these measures have been shown to be highly correlated (Holmqvist et al., 2011; Rudich-Strassler et al., 2022; Waechter et al., 2014). Finally, as free-viewing is the most widely used eye-tracking paradigm in visual attention research, considered as the most reliable and ecologic-valid (Armstrong and Olatunji, 2012; Lazarov et al., 2019), a secondary

<sup>&</sup>lt;sup>1</sup> Importantly, RT-based attentional tasks, including both the dot-probe and the Stroop task, exhibit poor psychometric properties (Eide et al., 2002; In-Albon and Schneider, 2010; Rodebaugh et al., 2016; Schmukle, 2005; Staugaard, 2009; Strauss et al., 2005; Waechter et al., 2014; Waechter and Stolz, 2015).

analysis was performed including free-viewing attentional studies only (Clauss et al., 2022).

#### 2. Method

The systematic review and meta-analysis protocol were registered in Prospero before undertaking the review and meta-analysis (Basel et al., 2022), and the report conforms to PRISMA guidelines (Moher et al., 2009).

#### 2.1. Search strategy

Studies were selected following a systematic search for publications between 1980, when OCD was first introduced in the DSM (American Psychiatric Association, 2013), and May 2022, in PubMed, PsycINFO, MEDLINE, PsycNet, and Web of Science. All relevant subject headings and free-text terms were used to represent OCD and eye-tracking in search strategies (see Supplemental material for detail). Reference sections of review articles, book chapters and studies selected for inclusion were searched for further studies.

#### 2.2. Search selection process

Titles and abstracts were independently screened by two reviewers (DB and HH) using the Covidence systematic review software (Babineau, 2014), based on the inclusion and exclusion criteria outlined below. Discrepancies were resolved by discussion between the two reviewers. Full articles were then independently screened by the same two reviewers. Where disagreements occurred, a consensus meeting was held to decide on study inclusion. Study selection process and reasons for exclusions are described in Fig. 1 (for the list of studies see Supplemental material).

We included studies if they: (1) used eye-tracking methodology; (2) assessed OCD symptoms using an accepted measure of OCD or a clinician diagnosis; (3) compared performance of at least two groups that differed on OCD symptoms or diagnosis<sup>2</sup>; (4) assessed attention to OCD-related stimuli as compared with neutral non-OCD stimuli. Studies were excluded on the following grounds: (1) review article, case study, or book chapter; (2) clinically-relevant symptoms of OCD were not used in defining study groups; (3) the OCD group was not specifically identified; (4) lack of a non-OCD control group; (5) participants had comorbid traumatic brain injury (TBI); and (6) studies were not originally designed to examine attentional biases in OCD.

#### 2.3. Data extraction and assessment of study quality

Data extraction and quality assessment were undertaken by two reviewers (DB and HH) and checked by a third (AL) for errors. Study characteristics extracted from reviewed studies included: (1) clinical status of the OCD group (clinical v. subclinical) and OCD measures used to define OCD; (2) comparison group (anxiety controls v. healthy controls); (3) OCD subtype; (4) stimulus type used (faces, pictures, words; pictures refers to images of scenes or objects); (5) stimulus specificity (OCD-related, general negative/threat); (6) stimulus valence (threat, neutral); (7) stimuli array size; (8) presentation duration; and (7) type of attentional variable examined (first fixation location, latency, total dwell time, fixation count).

Quality assessment was conducted independently by two reviewers (DB and HH) following a method previously employed in a systematic review of attention biases in generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD) which involved similar experimental designs (Goodwin et al., 2017; Lazarov et al., 2019). Specifically, the following criteria were used: Selection bias assessed the inclusion criteria used, accounting for confounding factors. Information bias measured whether studies used validated and reliable methods of assessment in relation to both the assessment of participants at recruitment (i.e. measures used to assess OCD symptomology and create the experimental groups) and the outcome measurement (i.e. the quality and characteristics of the eye-tracking apparatus used to record eyedata). Performance bias was evaluated in relation to the appropriateness of the experimental procedure used in the study to examine attentional processes. Finally, attrition bias was determined based on whether studies reported or accounted for dropouts/data loss. In representativeness, we considered whether the sample was selected from a group representative of the population aimed by the study, and in the statistical analysis, we determined whether the statistics and conclusions were appropriate and checked whether null results were also reported. As in the above-cited reviews (Goodwin et al., 2017; Lazarov et al., 2019), in determining study quality we considered the extent to which relevant confounding variables were controlled for. This was particularly important with regards to age, which has been shown to correlated with changes in attention processes as assessed using eye-tracking methodology (Isaacowitz and Choi, 2012; Knight et al., 2007; Nikitin and Freund, 2011). We also emphasized the clinical status of the OCD group and the groups' sample size in determining study quality (Lazarov et al., 2019).

#### 2.4. Data analysis

We analyzed the data using Comprehensive Meta-Analysis, Version 3 (CMA; Borenstein et al., 2015). Hedges' g was used as the effect size measure. We performed three separate meta-analyses. Two analyses focused on attentional vigilance, one with latency to first fixation and the other with first fixation location as the relevant dependent measure. The third analysis focused on attentional maintenance, with the dependent variable consisting of total dwell time and fixation count as a combined measure of attentional maintenance.<sup>3</sup> The interaction effect, reflecting a different attention allocation pattern to OCD-related and neutral stimuli between the OCD and control groups, was calculated based on a mixed-effect model, as recommended by Borenstein and his colleagues (Borenstein, 2019; Borenstein et al., 2009). As described earlier, as free-viewing is the most widely used attentional paradigm, also considered the most psychometrically sound (Armstrong and Olatunji, 2012; Lazarov et al., 2019), a secondary analysis was performed including free-viewing attentional studies only (Clauss et al., 2022).

The extent of a possible publication bias (Sterne et al., 2001) for significant interactions was explored separately for neutral and OCD-related stimuli, using funnel plots with the two-tailed Egger tests (Egger et al., 1997). As the systematic search yielded nine articles per eye-tracking measure (see Results below), of which eight were included in the meta-analysis, funnel plot asymmetry was only evaluated visually, as statistical tests for funnel plot asymmetry are unreliable with fewer than ten studies (Tarsilla, 2010).

#### 3. Results

The present meta-analysis aimed to examine whether individuals

<sup>&</sup>lt;sup>2</sup> In the study of Cludius et al. (2019), two comparisons were made. First, the control group was compared to the OCD group as a whole, using checking- and contamination-related stimuli. Next, the control group was compared, separately, to individuals with high checking symptoms (using checking-related stimuli) and high contamination symptoms (using contamination-related stimuli). To increase sample specificity and avoid reusing the same data we included only the latter in the present meta-analysis.

<sup>&</sup>lt;sup>3</sup> The combined measure of attentional maintenance was computed using the Comprehensive Meta-Analysis, Version 3 software (CMA; Borenstein et al., 2015), by calculating a mean effect size of the two variables (i.e., total dwell time and fixation count).



Fig. 1. PRISM flowchart of paper selection.

with OCD symptoms, as compared to non-OCD participants, demonstrate a heightened attentional bias towards OCD-related stimuli over neutral stimuli. In meta-analyses, the relevant statistic for answering this question is the Z-value that denotes the difference between groups in attention allocation to OCD-related vs. neutral stimuli. In other words, this Z-value reflects the magnitude of the interaction between group (OCD vs. control) and stimulus type (OCD-related vs. neutral).

Notably, this *Z*-value is likely to be an underestimation of the true effect statistic, as it assumes a zero correlation between the neutral and the OCD-related stimuli (Borenstein et al., 2015). As exemplified in Tables S1 and S2 (see Supplementary Material), as the assumed correlation coefficient increases, so does the Z value, and the associated *p*-value decreases. In eye-tracking studies in which the differently valenced stimuli are presented simultaneously (see Inclusion criterion 4), the viewing pattern of one stimulus is, by definition, related to the

viewing pattern of the other stimuli in the display. For example, if a specific display containing two stimuli is shown for 6 s, and the participant spends 4 s fixating on one stimulus, then the maximum time that can be spent fixating on the alternative stimulus will be 2 s. Thus, for each interaction analysis we also provide the significance parameters (both the Z score and the associated p-value) per assumed correlation coefficient between the neutral and the OCD-related stimuli (see Table 1 for a summary of the minimum required correlation for significance per measure and analysis).

#### 3.1. Systematic search

Our initial search yielded 712 potential records after removing duplications (see Fig. 1 for the PRISMA flowchart of paper selection). Records were then screened using titles and abstracts and those deemed

#### Table 1

Minimum required correlation for significance per measure and analysis.

	Vigilance	Vigilance	Maintenance
	(Latency to 1st	(1st fixation	
	fixation)	location)	
Main analysis	NS for any r	$r \ge 0.3$	$r \ge 0.9$
Exploratory analysis	NS for any r	$r \ge 0.8$	$r \ge 0$

*Note.* NS = not significant.

irrelevant (e.g., not examining OCD, not using eye-tracking methodology) were excluded (n = 666), resulting in 46 records that underwent full-text assessment. Records were then removed per inclusion/exclusion criteria (for specific reasons see Fig. 1). After a full-text review, eight journal articles (Armstrong and Olatunji, 2012; Armstrong et al., 2010; Botta et al., 2018; Carbonella and Timpano, 2016; Choi and Lee, 2015; Cludius et al., 2019; Mullen et al., 2021; Toh et al., 2017) and one doctoral dissertation (Harper, 2020) emerged as eligible records, for a total of nine records. Unfortunately, the study of Toh et al. (2017) had to be excluded from the meta-analysis phase due to missing essential data, following several failed attempts to contact the authors for these data. Thus, the final number of studies included in the meta-analysis was reduced from nine to eight. Study characteristics are presented in Table 2, and summaries of each study's results are provided in Table 3.

#### 3.2. Meta-analysis

#### 3.2.1. Vigilance

3.2.1.1. Latency to first fixation. The Z-value of the main analysis was not statistically significant, Z = 0.60, p = 0.55 (g = -0.09, CI = [-0.51, 0.32], p = 0.65, for the neutral stimuli; g = -0.27, CI = [-0.68, 0.14], p = 0.19, for the OCD-related stimuli), which was also the case for the secondary analysis of free-viewing studies only, Z = 0.46, p = 0.64 (g = -0.11, CI = [-0.75, 0.52], p = 0.73, for the neutral stimuli; g = -0.33, CI = [-0.96, -0.31], p = 0.31, for the OCD-related stimuli). For both analyses, the Z value did not reach significance at any correlation coefficient.

3.2.1.2. First fixation location. The Z-value was not statistically significant for the main analysis, Z = -1.66, p = 0.09 (g = -0.07, CI = [-0.36, 0.21], p = 0.61, for the neutral stimuli; g = 0.24, CI = [0.00, 0.48], p = 0.047, for the OCD-related stimuli). As can be seen in Table S1a, however, this Z-value becomes significant when the correlation between the neutral and the OCD-related stimuli exceeds 0.3 (yielding a Z value of -1.97), indicating a significant group-by-stimulus interaction with OCD participants showing a vigilance pattern favoring OCD-related over neutral stimuli to a larger extent than control participants (see Fig. 2).

The Z-value for the secondary analysis was also non-significant, Z = -1.00, p = 0.31, (g = -0.32, CI = [-1.07, 0.43], p = 0.40, for the neutral stimuli; g = 0.17, CI = [-0.43, 0.78], p = 0.57, for the OCD-related stimuli), with the group-by-stimulus type interaction becoming significant only from an assumed correlation between the neutral and the OCD-related stimuli of 0.8, yielding a Z value of 2.15 (see Table S1b), which seems unlikely.

*3.2.1.3. Publication bias.* The funnel plot for OCD-related and the neutral stimuli data in studies included in the main analysis (see Fig. S1) did not suggest a small study effect, that is, studies with smaller sample size did not yield larger effect sizes for vigilance (as assessed via first fixation location).

#### 3.2.2. Maintenance

The Z-value of the main analysis was not significant, Z = -0.76, p = 0.45 (g = -0.02, CI = [-0.31, 0.28], p = 0.91, for the neutral stimuli; g

= 0.15, CI = [-0.14, 0.44], p = 0.33, for the OCD-related stimuli). As seen in Table S2a, the Z-value becomes significant only at an assumed correlation of 0.9 (yielding a Z value of -1.97), which is extremely unlikely.

Conversely, our secondary analysis (See Fig. 3 and Table S2b) yielded a significant group-by-stimulus type interaction at any assumed correlation, Z = -2.71, p < 0.01, indicating different attention allocation patterns of the two groups to the neutral and the OCD-related stimuli (g = -0.30, CI = [-0.60, 0.00], p = 0.05, for the neutral stimuli; g = 0.29, CI = [-0.01, 0.59], p = 0.06, for the OCD-related stimuli). These trend-level simple effects indicate that compared to control participants, OC participants allocate more attention towards OCD-related stimuli, and less attention towards neutral stimuli.

*3.2.2.1. Publication bias.* The funnel plot for OCD-related and the neutral stimuli data in studies included in the secondary analysis (see Fig. S2) did not suggest a small study effect for attentional maintenance.

#### 3.3. Quality of studies

Five studies were of acceptable quality (Armstrong et al., 2010; Armstrong et al., 2012; Cludius et al., 2019; Harper, 2020; Mullen et al., 2021), one was rated as having good quality (Botta et al., 2018), and two as having low quality (Carbonella and Timpano, 2016; Choi and Lee, 2015). The 'good quality' study was rated as such due to two primary considerations. First, it employed a clinical OCD sample, using both an OCD-specific measure (i.e. OCI-R) and a general clinical interview (i.e. MINI version 5.0.0) to support the OCD diagnosis and asses co-morbid conditions (representativeness). Second, this study controlled for age as a possible confound, as well as for other elements such as gender and ethnicity (selection bias). While an additional study (Cludius et al., 2019) also met these two primary considerations, it employed a small sample size, which reduced its quality from 'good' to 'acceptable' (statistical analysis criterion). Studies that did not support OCD clinical status with a clinical interview (Mullen et al., 2021), or that included sub-clinical analogue samples (Armstrong et al., 2010; Armstrong et al., 2012; Harper, 2020), were considered of acceptable quality, unless other indications compromised this rating. Accordingly, while using a well-validated and reliable method of assessment, the study of Carbonella and Timpano (2016) did not control for age, or report statistics regarding age differences between groups. In addition, no information was provided regarding within-group gender distribution. Choi and Lee (2015) received a low-quality rating for failing to control for potential confounds other than age, such as gender and ethnicity (selection bias), and for including sub-clinical OCD participants.

#### 4. Discussion

The current review and meta-analysis explored attention processes in OCD as indicated by eye-tracking studies, as was previously done in other psychopathologies (Suslow et al., 2020; Chen and Clarke, 2017; Lazarov et al., 2019; Clauss et al., 2022), but not in OCD. Specifically, we examined whether individuals with high levels of OCD symptoms demonstrate a heightened tendency to allocate attentional resources to OCD-related stimuli, relative to neutral ones. Three separate metaanalyses were performed - two of attentional vigilance, via latency to first fixation and first fixation location, and one of attentional maintenance, using a combined measure of total dwell time and fixation count. These analyses were then repeated, including only free-viewing attentional studies. We found no significant effects for vigilance when assessed via latency to first fixation in either the main or the secondary analysis. For vigilance via first fixation location, the group-by-stimulus type interaction was significant, assuming a correlation of at least 0.3 between the neutral and the OCD-related stimuli, which, as explained above, is quite plausible. Including only free-viewing studies showed the

#### Table 2

Systematic review summary of study characteristics.

Study (Manuscript type)	OCD group (Sample size)	Control group	OCD diagnosis measures (General measure)	M:F ratio	Age mean ( <i>SD</i> )	OCD type/population	Ethnicity	Comorbidity (OCD group)
Armstrong et al. (2010) Journal article	HCF ( <i>n</i> = 23)	LCF (n = 25)	OCI-R - washing score only, PI- contamination fear subscale	HCF = 5:18 LCF = 10:15	HCF = 18.95 (0.90) LCF = 19.17 (1.27)	Contamination fears	Not reported	Not reported
Armstrong et al. (2012) Journal article	HCF ( <i>n</i> = 19)	LCF (n = 20)	PI-contamination fear Subscale, DS-R	HCF = 6:13 LCF = 13:7	HCF = 19.25 (1.02) LCF = 19.26 (0.81)	Contamination fears	HCF = 85 % Caucasian LCF = 79 % Caucasian	Not reported
Botta et al. (2018) Journal article	Clinical (n = 36)	HC (n = 36)	MINI, Y-BOCS	OCD = 14:22 HC = 14:22	OCD = 37.3 (13.3) HC = 37.2 (13.2)	Heterogeneous	Not reported	Entire sample = 72.2 % MDD (past comorbidity), 19.4 % social anxiety disorder, 8.3 % GAD, 2.7 % pathological gambling, 2.7 % bipolarity
Carbonella and Timpano (2016) Journal article	HHS ( <i>n</i> = 35)	LHS ( <i>n</i> = 34)	SIR	Entire sample = 18:51	19.4 (3.2)	Hoarding	Not reported	Not reported
Choi et al. (2015) Journal article	HCS (n = 35)	LCS (n = 34)	MOCI-checking subscale, PI- Checking subscale	Not reported	HCH = 21.89 (1.81) LCH = 22.82 (2.11)	Checking	Not reported	Not reported
Cludius et al. (2019) Journal article	Clinical ( $n = 28$ ; high contamination fear, n = 20, high on checking $n = 18$ )	HC ( <i>n</i> = 22)	MINI, Y-BOCS, OCI-R	OCD = 8:20 HC = 9:13	OCD = 39.29 (13.81) HC = 40.09 (15.03)	Contamination Checking (the 28 patients were divided to high and low on checking and contamination)	Not reported	Entire sample = 28.5 % MDD, 17.8 % dysthymia, 7.1 % panic disorder, 14.2 % agoraphobia, 7.1 % social anxiety disorder, 7.1 % GAD, 10.7 % Specific phobia
Harper (2020) <sup>a</sup> PhD Thesis	HCF ( <i>n</i> = 21)	LCF (n = 21)	OCI-R, YBOCS-SR	HSC = 8:13 LSC = 8:13	HSC = 24 (7.74) LSC = 24 (6.10)	Contamination	Not reported	Not reported
Mullen et al. (2021) Journal article	Clinical (n = 16)	HC ( <i>n</i> = 16)	OCI-R, YBOCS-SR	OCD = 7: 9 HC = 7:9	OCD = 37.06 (12.88) HC = 36.75 (13.34)	Heterogeneous	Not reported	Not reported
<sup>b</sup> Toh, Castle & Rossell (2017) Journal article	Clinical (n = 19)	HC (n = 21)	MINI, Y-BOCS	OCD = 26.3:73.7 HC = 38.1:61.9	OCD = 37.0 (10.4) HC = 35.7 (10.6)	Heterogeneous	Not reported	OCD sample = 8.8 % Depression, 15.2 % Social anxiety

Note. OCD = obsessive compulsive disorder; M:F = male:female; HCF = high contamination fear; LCF = low contamination fear; OCI-R = Obsessive Compulsive Inventory; PI = The Padua Inventory; DS-R = Disgust Scale; HC = healthy control; MINI = Mini International Neuropsychiatric Interview; Y-BOCS = Yale-Brown obsessive compulsive scale; HHS = high hoarding symptoms; LHS = low hoarding symptoms; SIR = Saving Inventory–Revised; HCS = high checking symptoms; LCS = low checking symptoms; MOCI = Maudsley Obsessive Compulsive Inventory; YBOCS-SR = Y-BOCS self-report.

<sup>a</sup> This study is a PhD thesis.

<sup>b</sup> This study emerged in the systematic search but was not included in the meta-analysis due to missing data required for analysis.

required correlation to increase to 0.8. For sustained attention, an opposite pattern emerged. The group-by-stimulus type interaction was significant in the main analysis only when assuming an extremely high correlation of 0.9. Conversely, when including free-viewing studies only, this interaction emerged as significant at any assumed correlation ( $r \ge 0$ ).

for first fixation location, but not for latency) might shed some light on the inconsistent findings of RT-based attentional research in OCD (Amir et al., 2009; Foa et al., 1993; Harkness et al., 2009; Kampman et al., 2002; Kyrios and Iob, 1998; Moritz et al., 2004; Rao et al., 2010; Tata et al., 1996; Van den Heuvel et al., 2005). As RT-based attentional tasks index attentional vigilance based on a specific moment in time (i.e., the keypress; a "snapshot" within the attentional process), attention can be

The results of our main analysis regarding vigilance (i.e., evidence

#### Table 3

Systematic review summary of study findings.

Study	Task	Stimuli type	OCD specificity of threat stimuli?	Additional stimuli (GNS, PS)?	Array size	Display time	Sampling rate (Hz)	Outcome measures	Results – attention bias to OCD-related stimuli?
Armstrong et al. (2010) Journal article	FV	Faces (disgust, fear, happy, neutral)	Yes (disgust)	GNS = N PS = N	2 faces (disgust-neutral, fear- neutral, happy- neutral)	3 s	60 Hz	1. First fixation location 2. Latency to first fixation 3. Total dwell time	<ol> <li>Y (fear faces, but no longer sig. when controlling trait anxiety)</li> <li>N</li> <li>Y (fear and disgust faces)</li> </ol>
Armstrong et al. (2012) Journal article	FV	Images (contamination, general threat, pleasant, neutral)	Yes (contamination)	GNS = Y PS = Y	4 images (contamination threat + general threat + pleasant + neutral)	30 s	60 Hz	<ol> <li>First</li> <li>First</li> <li>fixation</li> <li>location</li> <li>Duration</li> <li>of first</li> <li>fixations</li> <li>Total</li> <li>dwell time</li> <li>total</li> <li>number of</li> <li>fixations</li> <li>Average</li> <li>fixation</li> <li>lengths</li> </ol>	1. Y (contamination- related images) 2. N 3. N 4. N 5. Y (contamination- related images)
Botta et al. (2018) Journal article	vs	Word list (orthographic, semantic, obsession- related, neutral)	Yes (obsession- related list)	$\begin{array}{l} GNS=N\\ PS=N \end{array}$	13 words-A target word, 6 distractor words and 6 "target- unrelated" (filler) words	Until response (mouse click)	50 Hz	1. Number of fixations on non- target words 2. Mean duration of fixations on non-target words	1. Y (neutral and semantic lists) 2. N
Carbonella and Timpano (2016) Journal article	CFT	Images (hoarding- related, nature related, blank control)	Yes (hoarding images)	GNS = N PS = N	1 distractor per trial: Hoarding/nature/ blank	Stimuli were presented until either a response was provided or 3 s had elapsed	Not reported	<ol> <li>First fixation location (distractor vs target)</li> <li>Total dwell time</li> </ol>	1. N 2. N
Choi et al. (2015) Journal article	FV (and before a classification task in order to manipulate responsibility feeling)	Words (OC- related threat, negative, positive, neutral)	Yes (OC-related words of checking)	GNS = Y PS = Y	3 pairs of words one after another (OC threat-neutral/ negative-neutral/ positive-neutral)	3 s per pair × 3 (9 overall)	60 Hz	<ol> <li>First</li> <li>fixation</li> <li>location</li> <li>Latency</li> <li>to first</li> <li>fixation</li> <li>Total</li> <li>dwell time</li> </ol>	1. 1. Y-(OC- related words) 2. N 3. N
Cludius et al. (2019) Journal article	FV	Images (contamination, checking, neutral)	Yes (contamination, checking)	$\begin{array}{l} GNS = N \\ PS = N \end{array}$	2 images (Contamination- neutral, Checking–neutral)	5 s	120 Hz	<ol> <li>Latency to first fixation</li> <li>Total dwell time</li> </ol>	<ol> <li>N</li> <li>Y (checking- related images)</li> </ol>
Harper (2020) Thesis	Dot-probe	Images (general threat, contamination threat, neutral) Words (general aversive, contamination threat, neutral)	Yes (contamination images)	GNS = Y PS = N	2 images/words (General threat image BW-neutral image BW, Contamination threat image BW- neutral image BW- neutral image BW- (General threat image COLOR, neutral image COLOR, Contamination threat image COLOR, neutral image COLOR, General aversive word- neutral word, Contamination threat word-neutral word)	2.5 s	250 Hz	1. First fixation location 2. Latency to first fixation 3. Average duration of initial fixation 4. Total dwell time 5. Total frequency of fixations	1. N 2. N 3. N 4. N 5. N

(continued on next page)

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#### Table 3 (continued)

Study	Task	Stimuli type	OCD specificity of threat stimuli?	Additional stimuli (GNS, PS)?	Array size	Display time	Sampling rate (Hz)	Outcome measures	Results – attention bias to OCD-related stimuli?
Mullen et al. (2021) Journal article	FV	Images (OCD- related: contamination, checking, symmetry, hoarding; general threat, neutral)	Yes (contamination, checking, symmetry, hoarding)	$\begin{array}{l} GNS = Y \\ PS = N \end{array}$	2 images (Contamination- neutral, Checking- neutral, Symmetry-neutral, Hoarding-neutral, General threat- neutral)	2 s	250 Hz	<ol> <li>First fixation location</li> <li>Latency to first fixation</li> <li>Duration of first fixation</li> <li>Total number of fixations</li> <li>Total dwell time</li> </ol>	1. N 2. N 3. N 4. Y (general threat and OCD- related) 5. (General threat and OCD- related)
<sup>®</sup> Toh, Castle & Rossell (2019) Journal article	Card version of the Emotional Stroop task	Seven 10-word lists: (i) BDD-positive (ii) BDD-negative (iii) OCD- checking (iv) OCD-washing (v) general positive (vi) general threat (vii) neutral	Yes (OCD washing-, OCD- checking)	GNS = Y PS = Y	10-word list (7 options)	NR	500 Hz	<ol> <li>Number of blinks</li> <li>Number of fixations</li> <li>Fixation duration</li> <li>Saccade amplitude</li> </ol>	1. N 2. N 3. N 4. N

Note. OCD = obsessive compulsive disorder; FV = free viewing; GNS = general negative stimuli; PS = positive stimuli; Y = yes; N = no; s = seconds; Hz = hertz; HCF = high contamination fear; LCF = low contamination fear; VS = visual search; CFT = Cognitive Flexibility Task; HHS = high hording symptoms; LHS = low hoarding symptoms; OC = obsessive compulsive; BW = black-white.

<sup>a</sup> This study emerged in the systematic search but was not included in the meta-analysis due to missing data required for analysis.

Study name	Comparison		Statis	stics for e	ach stud	ły				Hedges's g and 98	5% CI	
		Hedges's g	Standard error	Lower limit	Upper limit	Z-Value	p-Value					
Armstrong et al. 2012	NE	-0.276	0.315	-0.894	0.342	-0.876	0.381	1	I-		1	
Carbonella & Timpano 2016	NE	0.143	0.230	-0.307	0.594	0.624	0.533				-	
Harper 2020- images	NE	-0.150	0.303	-0.745	0.444	-0.496	0.620			∎	-	
Harper 2020- words	NE	0.093	0.303	-0.500	0.687	0.308	0.758				<u> </u>	
Mullen et al. 2021	NE	-0.369	0.348	-1.050	0.313	-1.061	0.289					
		-0.063	0.130	-0.318	0.192	-0.486	0.627			-		
Armstrong et al. 2010	CCD	0.000	0.284	-0.557	0.557	0.000	1.000				-	
Armstrong et al. 2012	CCD	0.926	0.331	0.278	1.575	2.799	0.005			-	<b>e</b>	
Carbonella & Timpano 2016	CCD	0.134	0.230	-0.317	0.584	0.580	0.562				-	
Choi & Lee 2015	CCD	0.552	0.243	0.077	1.028	2.276	0.023					
Harper 2020- images	CCD	0.178	0.303	-0.417	0.772	0.586	0.558					
Harper 2020- words	CCD	0.227	0.304	-0.368	0.823	0.748	0.454					
Mullen et al. 2021	OCD	-0.402	0.348	-1.085	0.280	-1.155	0.248					
		0.245	0.107	0.036	0.455	2.294	0.022				•	
								-2.00	-1.00	0.00	1.00	

**Fig. 2.** Forest plot of the main analysis depicting effect sizes for the neutral and OCD-related stimuli – first fixation location. *Note.* Negative values of Hedges' g indicate lower scores of OCD participants as compared to control participants. *NE* = neutral stimuli, *OCD* = OCD-related stimuli; *images* = stimuli consisted of images, *words* = stimuli consisted of images.

only inferred indirectly from facilitated or interfered performance. Thus, RT-based tasks are inherently limited in their ability to distinguish between different aspects of attention, especially within single trials (Armstrong et al., 2013; Cisler and Koster, 2010; Lazarov et al., 2019). Thus, it remains unclear whether it is the speed of attention orienting or the direction of orienting which accounts for observed results, with only eye-tracking research being capable of separating the two (Clauss et al., 2022; Lazarov et al., 2019). Moreover, unlike eye-tracking, RT-based tasks rely on keypresses as indices of attention, giving rise to potential confounding elements related to the execution of the required motor responses (i.e., key-presses), possibly obscuring the underlying process of emergent results (Armstrong and Olatunji, 2012; In-Albon et al., 2010; Kimble et al., 2010; Price et al., 2016; Thomas et al., 2013). Present findings suggest it is the direction of orienting which accounts for observed results, not the speed of attention orienting. Further zooming in on first fixation location, our secondary analysis of freeviewing tasks yielded no evidence for vigilance (i.e., the assumed correlation for significance increased from 0.3 to 0.8), suggesting that present results were mainly driven by studies using non-free-viewing tasks.

In contrast to the first fixation location, significant effects for attentional maintenance emerged only after excluding non-free-viewing studies, as the required correlation for significance dropped from 0.9 to zero. The lack of attentional maintenance in non-free-viewing studies is

Study name	Comparison	Statistics for each study							
		Hedges's g	Standard error	Lower limit	Upper limit	Z-Value	p-Value		
Armstrong et al. 2010	NE	-0.823	0.296	-1.404	-0.243	-2.779	0.005		
Armstrong et al. 2012	NE	0.130	0.314	-0.486	0.746	0.413	0.680		
Cludius et al. 2019- ch	NE	-0.411	0.315	-1.028	0.207	-1.304	0.192		
Cludius et al. 2019- con	NE	0.028	0.303	-0.566	0.622	0.091	0.927		
Mullen et al. 2021	NE	-0.428	0.355	-1.124	0.267	-1.207	0.227		
		-0.303	0.155	-0.606	0.000	-1.959	0.050		
Armstrong et al. 2010	OCD	0.311	0.286	-0.250	0.871	1.087	0.277		
Armstrong et al. 2012	OCD	-0.035	0.314	-0.650	0.581	-0.110	0.912		
Cludius et al. 2019- ch	OCD	0.442	0.315	-0.176	1.060	1.401	0.161		
Cludius et al. 2019- con	OCD	0.100	0.303	-0.494	0.695	0.331	0.741		
Mullen et al. 2021	OCD	0.731	0.359	0.027	1.435	2.036	0.042		
		0.290	0.154	-0.011	0.592	1.886	0.059		



**Fig. 3.** Forest plot of the secondary analysis depicting effect sizes for the neutral and OCD-related stimuli – attentional maintenance. *Note.* Negative values of Hedges' g indicate lower scores of OCD participants as compared to control participants. NE = neutral stimuli, OCD = OCD-related stimuli; ch = participants with high score on the OCI-R checking subscale, con = participants with high score on the OCI-R checking subscale, con = participants with high score on the OCI-R contamination fear subscale.

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further supported by the study of Toh et al. (2017), which was excluded from the meta-analysis due to missing essential data for analysis. Using an eye-tracking-based emotional Stroop task, comprised of OCD-related (checking, washing) and neutral words, the authors found no evidence for attention maintenance to OCD-related words, as assessed via both number of fixations and mean fixation duration per word type (Toh et al., 2017). Importantly, unlike vigilance, attentional maintenance cannot be assessed via RT-based tasks, as these tasks provide no information about the course of attention deployment before or after the moment of measurement (Armstrong and Olatunji, 2012; Lazarov et al., 2016; Lazarov et al., 2019), which is essential for detecting sustained attention. Thus, only eye-tracing-based tasks can actually assess this attentional feature.

What might explain the divergence in results between free-viewing and non-free-viewing eye-tracking tasks of attention allocation in OCD? One possible explanation might be the nature of tasks used - while free-viewing tasks pose no requirements for participants (other than viewing what is presented in front of them), non-free-viewing tasks entail specific demands and/or goals. For example, participants may be required to search for a specific target situated within several distractors (visual search task), or to react to the direction of a probe which appears after viewing specific stimuli (dot-probe task). Here, unlike in freeviewing tasks, participants must hold information related to task demands in memory to perform adequately. Indeed, research has shown OCD to be characterized by cognitive/executive deficits, including working memory impairments (Abramovitch et al., 2013; Abramovitch and Cooperman, 2015; Goncalves et al., 2016; Harkin et al., 2020; Tubío Fungueiriño et al., 2020). Considering present results, it is possible that attentional vigilance can only be evident when memory/cognitive load is heightened, giving rise to more automatic processes of attention orienting (Armstrong and Olatunji, 2012; Corbetta and Shulman, 2002; Posner and Petersen, 1989). Hence, a task with no specific demands, such as free-viewing, may be less suitable for detecting this attentional component (Lazarov et al., 2019), which may simply not exist in this context (Bradley et al., 2016; Cludius et al., 2019; Mullen et al., 2021). Conversely, when no demands exist more cognitive resources are available, giving rise to goal-oriented attentional processes such as attentional maintenance (Armstrong and Olatunji, 2012; Corbetta and Shulman, 2002; Posner and Petersen, 1989), which can be more readily explored.

The current review has several limitations. First, we decided not to include correlational studies (see Basel et al., 2022 for the preregistration information of this study) to increase the accuracy of our research question, namely, whether individuals with high OCD symptomology *differ* from controls on OCD-related attentional processes. However, this may have resulted in the exclusion of studies which are relevant to the body of knowledge on attentional biases in OCD. For example, Bradley et al. (2016) found obsessive-compulsive symptoms to predict greater frequency and duration of fixations on OCD-related stimuli during a free-viewing task, with no finding supporting the vigilance bias, results which are in line with current findings. Second, as the utilization of eve-tracking research is relatively new, compared to more traditional RT-based attentional tasks, the number of studies included in this review and meta-analysis was relatively small, making it difficult to delineate more specific conclusions (needless to say, we had no advance knowledge of the final number of records that would emerge in the systematic search of extant literature). Still, we hope that the present paper will provide an initial roadmap for additional research in the field. Third, due to the heterogeneity of OCD symptomology, the included studies also varied in the nature of the examined samples (e.g., individuals high on fear of contamination symptoms, high on checking symptoms, patients with an OCD diagnosis). Relatedly, not all studies used OCD-related stimuli corresponding to the symptomology of the examined sample (e.g., using contamination-related stimuli with participants high on contamination fears), with one study using general non-OCD emotional stimuli such as faces (Armstrong et al., 2010). This may have reduced the power of these studies to detect significant findings while also limiting the specificity of the emerging results (De Mathis et al., 2020; Pergamin-Hight et al., 2015). Finally, wide heterogeneity in study design was also noted across the reviewed studies, which, as the present meta-analysis shows, may affect emergent results. In trying to address this, we conducted the secondary analysis of free-viewing studies only, which were indeed found to produce a different results pattern.

Current finding may have some implications for future research in the field. First and foremost, more eye-tracking-based research is clearly needed to further clarify attention processes and biases in OCD, taking into account task type and which attention feature is to be explored (as present findings show that different tasks may tap different attentional features). Second, most extant studies used simple displays of two competing stimuli presented at once (Armstrong et al., 2010; Cludius et al., 2019; Mullen et al., 2021; cf. (Armstrong et al., 2012)). More complex visual displays (e.g., two-by-two picture matrices) are needed to increase the generalizability of observed results (Lazarov et al., 2016; Richards et al., 2014), especially as gaze patterns have been shown to be affected by the size of the stimuli array (Richards et al., 2014; Yates et al., 2010). Third, future research should better match sample type (e. g., cleaners) and stimuli type (e.g., contamination-related cues) to maximize the power to detect attentional features differentiating individuals with OCD from non-OCD controls, which may exist (Pergamin-Hight et al., 2015). Fourth, the attentional feature of avoidance should be explored using a time-course analysis of eye-data (e.g., exploring total dwell time per consecutive time-epochs; Kimble et al., 2010; Felmingham et al., 2011), as no study to date has done so in OCD. Exploring

avoidance is imperative for gaining a more complete understanding of attention allocation processes (Weierich et al., 2008). Finally, all included studies used OCD-related threat stimuli (e.g., a turned-on stove) assumed to provoke corresponding obsessions (e.g., checking obsessions) due to their threatening nature. However, obsession-related anxiety is often followed by the performance of corresponding compulsive behaviors, leading to relief and decreased distress, even if short lived (Grant, 2014), reflective of negative-reinforcement processes (Denys, 2011; Basel and Lazarov, 2022). Thus, future research may wish to explore attention allocation to OCD-related stimuli that signal "endstates" of compulsive behavior (e.g., a clearly turned-off stove, or perfectly clean sink) which may yield different attentional patterns than those noted for traditionally-used OCD-related threat cues.

Present findings may also have clinical implications for current ABM efforts in OCD. As attention precedes behavior and guides higher-order thought processes (e.g., working memory and decision making, Desimone and Duncan, 1995; Feldmann-Wüstefeld et al., 2019), it has been suggested that modifying one's (biased) attention may also lead to a corresponding change in one's behavior, and to reduction in symptoms (Bar-Haim, 2010; Fodor et al., 2020). Unfortunately, extant ABM studies in OCD show only limited clinical efficacy (e.g., Habedank et al., 2017; Najmi and Amir, 2010; Rouel and Smith, 2018). Importantly, all ABM studies in OCD targeted biased attention as indexed by RT-based tasks (e.g., the dot-probe task), which, as stated above, are inherently limited in their ability to distinguish between the different components of the attentional process (Armstrong et al., 2013; Lazarov et al., 2019). This is crucial, however, for clarifying which specific aspects of attention might be affected, and hence should be targeted in treatment (Lazarov et al., 2021). Current findings implicate two potential more fine-grained targets for intervention - vigilance (as indexed by first fixation location) and maintenance (as indexed by either total fixation duration or count), with results further suggesting which task should be used for which attentional bias - tasks that entail specific demands and/or goals for vigilance, and free-viewing tasks for sustained attention. Future research on ABM in OCD could explore the clinical efficacy of a gaze-contingent ABM procedure (Lazarov et al., 2017; Shamai-Leshem et al., 2021) that would target one or both of the above-mentioned targets, using the suitable task per target.

#### Authors declaration

We declare that this manuscript is original and that it has not been published before or has been posted on a web site and that it is not currently being considered for publication elsewhere.

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#### CRediT authorship contribution statement

Dana Basel: Conceptualization, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. Hadar Hallel: Writing – original draft, Writing – review & editing. Reuven Dar: Writing – review & editing, Formal analysis. Amit Lazarov: Conceptualization, Funding acquisition, Investigation, Resources, Supervision, Writing – review & editing.

#### **Conflict of interest**

The other authors have no financial disclosures. We wish to confirm that there are no known potential conflicts of interest associated with this publication.

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#### Institutional board review

The authors assert that all procedures contributing to this work comply with APA ethical standards and with the Helsinki Declaration of 1975, as revised in 2008. All procedure were approved by the committees on human experimentation in Tel Aviv University.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.12.141.

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